

ANNALS OF INTERNAL MEDICINE

MAURICE C. PINCOFFS

Editor

VOLUME 15

(OLD SERIES, VOLUME XX)

July to December, 1941

Contents

NUMBER 1, JULY, 1941

Special Medical Service in the Defense Program	CHARLES S STEPHENSON	1
The Recruit's First Year	P. S. MADIGAN	18
Silent or Atypical Coronary Occlusion	WILLIAM D STROUD AND JOSEPH A WAGNER	25
The Effect of Thiamin on the Residual Neural Disturbances of Treated Pernicious Anemia	J C ZILLHARDT, KEITH MACLEAN and WILLIAM P. MURPHY	33
The Effect of Vitamin B Complex on the Residual Neural Disturbances of Treated Pernicious Anemia	J C ZILLHARDT, ISABEL HOWARD and WILLIAM P MURPHY	44
The Syndrome of Multiple Vitamin Deficiency	V P SYDENSTRICKER	45
Glucose-Sulfapyridine, Experimental and Clinical Studies	HERBERT K ENSWORTH, JAMES LIEBMANN, MERTON C LOCKHART and NORMAN PLUMMER	52
A Syndrome of Upper Esophageal Stenosis	MORTIMER R CAMIEL and LEO LOEWE	63
The Development of Plasma Preparations for Transfusions	MAX M STRUMIA and JOHN J MCGRAW	80
Toxic Depression of the Myeloid Elements Following Therapy with the Sulfonamides, Report of 8 Cases	SOLOMON S RINKOFF and MAXWELL SPRING	89
The Responsibility of the Hospital Staff in Graduate Medical Education	FRANK J SLADEN	108
Case Reports		
Thrombocytopenic Purpura Associated with Discoid Lupus Erythematosus and Renal Glomerular Changes	MORTON H EDELMAN	116
Myxedema Heart, Report of Case	ARTHUR H MASTER and JENNY STRICKER	123
Auricular Flutter of Eleven Years' Duration with Observations on Esophageal Electrocardiograms	CHARLES E KOSSMAN and A R BERGER	128
Myasthenia Gravis, A Discussion, with Presentation of a Case Associated with a Thymoma	SAMUEL F ARONSON	137
Editorial		146
Reviews		149
College News Notes		152

NUMBER 2, AUGUST, 1941

Industrial Hygiene in the National Defense Program	J. J. BLOOMFIELD	165
The Control of Infectious Diseases in Rapidly Mobilized Troops	A. P. HITCHINS	172
The Mechanisms of Peripheral Circulatory Failure	CARL J. WIGGERS	178
The Pneumonia of Friedlander's Bacillus	L. A. JULIANELL	190
Weil's Disease, Report of Three Cases, Including the Morbid Anatomy of One Case, and a Brief Review of the Pertinent Literature	JOEL J. WHITE and JOHN V. PREVOST	207
Therapeutic Studies in Hyperthyroidism	PAUL STARR and HERMAN POMERINSKI	226
Acute Hepatitis of Alcoholism: A Clinical and Laboratory Study	HORACE B. CATS	244
The Sigmoidoscopic Diagnosis of Periarteritis Nodosa	JOSEPH FLISSEN	251
Some Problems Confronting the Physician in the Examination of Automobile Drivers	LOWELL S. SEILING	265
Clinical Studies with the Aid of Radio-Phosphorus. III. The Absorption and Distribution of Radio-Phosphorus in the Blood of, Its Excretion by, and Its Therapeutic Effect on, Patients with Polycythemia	L. A. ELL and J. H. LAWRENCE	276
Experiences in the Treatment of Subacute Bacterial Endocarditis with Sulfonamide, Sulfapyridine and Sulfathiazole, A Review of Previously Reported Cured Cases with the Report of Fifteen Treated Cases, Including One Cure and One Aborted Case	HOWARD E. HAYCE and FORD K. HICK	291
The American Board of Internal Medicine as a Factor in Scholarship in American Medicine	ERNEST L. LEVINS	304
Index		

Results from the Management of Bleeding Gastric and Duodenal Ulcer T. GRILR MILLER	390
Weil's Disease; Report of Six Cases HOWARD K RATHBUN and JULIUS M WAGHELSTEIN	395
The Diagnosis and Management of Brucellosis WALTER M SIMPSON	408
The Sulfonamide Therapy of Staphylococcal Septicemia ROBERT G TORREY, L A JULIANELLE and H G McNAMEE	431
The Value of Sternal Marrow Aspiration as a Method of Bone Marrow Biopsy. ERNEST H FALCONER and MAURICE E LEONARD	446
Changes in the Cardiac Shadow Following Pharmacological "Shock" Therapy of Schizophrenia HAROLD W STERLING and CRAWFORD N BAGANZ	459
Electrocardiographic Changes in Stab and Gunshot Wounds of the Heart, with Review of the Literature J. SOLOVAY, G D RICE and H U SOLOVAY	465
Tachycardia and Sensitivity to Heat as Indications for Basal Metabolic Rate Determination ABE RAVIN	478
Clinical Studies with the Aid of Radio-Phosphorus IV The Retention in Blood, the Excretion and the Therapeutic Effect of Radio-Phos- phorus on Patients with Leukemia L A ERF, L W TUTTLE and J H LAWRENCE	487
Symptomatic Hemolytic Anemia KARL SINGER and WILLIAM DA- MESHEK	544
Experimental Exophthalmos and Associated Myopathy Induced by the Thyrotropic Hormone ROBERT B AIRD	564
The Responsibility of the American College of Physicians for Post- graduate Training EDWARD L BORTZ	582
Case Reports	
Rupture of Aorta into the Pulmonary Artery with Long Survival PAUL D WHITE, FRANCIS L CHAMBERLAIN and SAUL R KELSON	589
A Fatal Case of Besnier-Boeck-Schaumann's Disease with Autopsy Findings FREDERICK TICE and HENRY C SWEANY	597
<i>Micrococcus Tetragenus</i> Meningitis, Report of a Case and Review of the Literature JOHN E LEACH and FRED G MEDINGER	609
Editorial	617
Reviews	620
College News Notes	623

NUMBER 4, OCTOBER, 1941

Mass Immunization against Typhus Fever R E DYER	629
Cerebral Embolism in Mitral Stenosis ALFRED W HARRIS and SAMUEL A LEVINE	637

Pulmonary Infarction in Heart Disease. LAURENCE E. HINES and JORDAN T. HUNT	644
The Chemistry of Vitamin K. LOUIS F. FILSER	648
The State of Sensory and Motor Centers in Patients with Hypothyroidism. NORBERT ENZLER, ERNST SIMONSON and SAMUEL S. BLANKSTLIN	659
The Concept of Psychosomatic Rheumatism. JAMES L. HALLIDAY	666
Schizophrenia. A Neurobiologic Approach. ARTHUR O. HECKER	678
Plasma Creatinine Determination as a Test of Low Grade Kidney Damage. ABRAHAM ARKIN, HANS POPPER and FRIED A. GOLDBERG	700
Hunner Ulcer of the Bladder, Review of 100 Cases. CHARLES C. HIGGINS	708
A Roentgen Study of Cavities in Pulmonary Tuberculosis, Cavity Changes Under Collapse and Non-Collapse Measures. R. C. EDSON and A. L. STAPLEY	716
Idiopathic Cardiac Enlargement Occurring in Infants and Children. J. MARSHALL NIELLY	727
Case Reports.	
Cold Allergy, Report of an Unusual Case. WALLACE M. YATUP and EDWARD W. NICKLAS	713
Syphilitic Pan-Meningitis (So-Called Chronic Hypertrophic Spinal Pachymeningitis). GORDON R. KAMMAN and A. B. BAKER	718
Subacute Bacterial Endocarditis Caused by a Hitherto Undescribed Gram Negative Coccus. GUSTAVE J. DAMMIS	722

Screening for Tuberculosis in a Civilian Population by Fluorography BRUCE H DOUGLAS and CARL C. BIRKELO	853
Familial Acholuric Jaundice Associated with Bone Changes. ERIC L COOPLER	858
Neurological, Medical and Biochemical Signs and Symptoms Indicating Chronic Industrial Carbon Disulphide Absorption F H LEWIS	869
The Solubility of Acetylsulfapyridine and Acetylsulfathiazole in the Urine ARTHUR C CURTIS and SIDNEY S SOBIN	884
Arsenical Sensitivity and Vitamin C MAHLON H DELP and C J WEBER	890
Case Reports	
Long Standing Productive Cough as the Chief Clinical Manifestation in Mitral Stenosis, A Case Complicated by Thrombosis of Left Auricle ESTELLE E KLEIBER	899
Association of Postural Hypotension with Sympathetic Nervous System Dysfunction, Case Report, with Review of Neurologic Features Associated with Postural Hypotension RICHARD H YOUNG	910
Prerenal Uremia Due to Papilloma of the Rectum ROBERT W GARIS	916
Editorial	927
Reviews	931
College News Notes	933
1942 Program of Intensive Postgraduate Courses Arranged by the American College of Physicians	944

NUMBER 6, DECEMBER, 1941

The Clinical Symptoms and Signs of Vitamin B Complex Deficiency WILLIAM H SEBRELL	953
Scarlet Fever Immunization JOHN A TOOMEY	959
The Treatment of Acute Empyema, Treatment by Continuous Tidal Irrigation and Suction (Hart) BEN KLOTZ and BERNARD LIDMAN	974
Chemotherapy of Bacterial Endocarditis RALPH A KINSELLA	982
Sputum Studies in Pneumonia The Selection of Therapy ARTHUR W FRISCH and ALVIN E PRICE	987
The Medical Aspect of Ankylosing Spondylitis (Marie-Strumpell) W W HERRICK and T LLOYD TYSON	994
Rheumatism and Arthritis, Review of American and English Literature for 1940 (Eighth Rheumatism Review) PHILIP S HENCH, WALTER BAUER, EDWARD BOLAND, M HENRY DAWSON, RICHARD H FREY- BERG, W PAUL HOLBROOK, J ALBERT KEY, L MAXWELL LOCKIE and CURRIER MCEWEN	1002

Case Reports:

Echinococcus Cyst of the Heart; Report of a Case. C. J. ATTWOOD,
WILLIAM H. SARGENT and FELTHER TAYLOR 1109

Sensitivity to Peanut Oil with the Report of a Case FRANCIS H
CHAMBERLAIN 1116

Editorial . 1118

Reviews . 1119

College News Notes . 1122

Minutes of the Board of Governors 1156

Index . 1165

ANNALS OF INTERNAL MEDICINE

VOLUME 15

JULY, 1941

NUMBER 1

SPECIAL MEDICAL SERVICE IN THE DEFENSE PROGRAM¹

By Captain CHARLES S STEPHENSON (MC), U S Navy †

THE effects of war or preparation for defense have always posed special service problems for medical men, for wherever the armies of the many warring Nations have fought there also the soldier-surgeon-physician, men of genius like Ambrose Paré, Dominique Larrey, Sir John P. Pringle, Sir Ronald Ross, Major Walter Reed, and countless others, have carried their skills to the battlefields in an effort to prevent illness and to mitigate the suffering of the wounded.

The whole map of this World War is being so speedily reshaped by the ebb and flow of British naval might and German military power that it is of the utmost importance that at least a few of the special service problems confronting the military surgeon be catalogued and brought to the attention of the leaders in the civil medical profession, for without your cooperation, the Army and Navy medical officers will be handicapped.

The Franco-Prussian War of 1870 provides the first record of a war in which more men were lost from military action than from disease. A similar record was established in the Russo-Japanese War of 1904. Despite the epidemic of influenza in 1918, the World War I was the first war in which the forces of the United States had fewer deaths from disease than from battle casualties, although for the entire Army at home and overseas, the deaths from disease were preeminent.¹

In order to emphasize the importance of communicable diseases, it is well to review briefly some of the experiences of the 1914-1918 World War and to indicate what may be expected in event unfortunate contingencies force upon this Nation the mobilization of large numbers of men.

* Read at the Boston meeting of the American College of Physicians, April 24, 1941

† In Charge, Division of Preventive Medicine, Bureau of Medicine and Surgery, Navy Department, Washington, D C

In the United States Army * for the period 1914-1918, the largest number of primary admissions for the communicable diseases was recorded for influenza, venereal diseases, mumps and measles. Influenza, tuberculosis, measles, and cerebrospinal meningitis were the leading causes of death.

Table 1 shows the number of primary admissions, the rates per 1,000, and days lost from duty for the U. S. Army from April 1, 1917, through December 31, 1919, in all areas of the United States, Alaska, and Europe, exclusive of Russia. The total mean annual strength of the U. S. Army was 4,128,479, with 2,235,389 in the United States and 1,665,796 in Europe.

Table 2 contains the same information for the U. S. Navy for the calendar years 1917, 1918, and 1919.

Infections of the respiratory tract were among the leading causes of sickness and death in both the Army and the Navy during this period.

TABLE I (Continued)

	Primary Admissions		Days Lost from Duty	
	Number	Annual Rate per 1 000	Number Sick Days	Noneffective Ratio per 1,000 ²
Dysentery (all), diarrhea, enteritis, and colitis	92,512	22.4	1,060,229	7
United States	39,854	17.8	232,241	3
Europe	48,202	28.9	793,972	13
Tuberculosis of lungs	33,249	8.0	3,385,053	22
United States	27,274	12.2	2,636,722	32
Europe	4,877	2.9	677,169	11
German measles	17,378	4.2	211,645	1
United States	16,167	7.2	197,330	2
Europe	579	4	8,505	4
Malarial fevers (all)	15,555	3.8	194,529	1
United States	10,510	4.7	130,673	2
Europe	950	6	20,477	4
Scarlet fever	11,675	2.8	498,190	3
United States	9,038	4.0	382,628	5
Europe	2,370	1.4	106,877	2
Diphtheria	10,909	2.6	317,050	2
United States	5,884	2.6	144,452	2
Europe	4,860	2.9	168,100	3
Meningitis, cerebrospinal (epidemic)	4,831	1.2	268,164	2
United States	2,878	1.3	150,386	2
Europe	1,848	1.1	114,110	2
Chickenpox	1,757	4	31,534	4
United States	1,208	5	21,443	4
Europe	388	2	7,582	4
Typhoid fever	1,529	4	109,374	1
United States	546	2	28,587	4
Europe	885	5	76,649	1
Smallpox	853	2	24,275	4
United States	780	4	21,890	4
Europe	24	4	1,110	4
Trench fever	798	2	34,098	4
United States	11	4	674	4
Europe	786	5	33,402	4

¹ Total mean annual strength = 4,128,479, United States (including Alaska) = 2,235,389, Europe (excluding Russia) = 1,665,796, other (Philippine Islands, Panama, etc.) = 227,294

² Noneffective rate = $\frac{\text{total days lost} \times 1,000}{\text{total mean annual strength}} - 365$

³ Respiratory diseases include influenza, bronchitis, lobar and broncho-pneumonia and pneumonia, unclassified

⁴ Rate per 1,000 less than 0.1

Influenza, bronchitis, and pneumonia combined were responsible for 1,326,306 admissions, giving a rate of 256.21 per 1,000. There were 50,042 deaths, or a death rate of 9.67 per 1,000, and a case fatality rate of 3.8 per cent. These diseases accounted for 19,293,711 sick days during this period, or a noneffective ratio of 10.03 per 1,000*. The 10 diseases responsible for the greatest number of sick days in the Army and Navy are listed in table 3. A total of 39,082,365 sick days was recorded for these diseases.

* Reports of Surgeon General, U. S. Navy, for 1918, 1919, and 1920

TABLE II

Admissions and Days Lost from Duty for Certain Infectious Diseases, U. S. Navy, Calendar Years 1917, 1918, and 1919

Disease	Primary Admissions		Days Lost from Duty	
	Number	Annual Rate per 1,000	Number Sick Days	Aggregate Rate per 1,000
Respiratory diseases	200,950	191.73	2,250,873	5.87
Influenza	151,916	144.91	1,366,625	3.57
Bronchitis	32,525	31.03	374,989	0.98
Pneumonia (all)	16,518	15.76	509,259	1.33
Venereal diseases (all)	90,700	86.53	1,248,188	3.26
Gonococcus infection	56,155	53.58	647,326	1.69
Syphilis	13,350	12.74	598,558	1.01
Chancroidal infections	20,995	20.03	602,301	0.53
Mumps	33,485	31.95	630,126	1.61
Measles	15,687	14.97	121,909	0.59
Dysentery (all), diarrhea, enteritis and colitis	6,399	6.11	67,916	0.18
Tuberculosis	4,180	3.99	59,683	1.49
German measles	6,380	6.10	4,998	0.22
Malarial fever (all)	7,327	6.99	103,257	0.27
Scarlet fever	2,594	2.47	102,817	0.27
Diphtheria	2,858	2.73	5,522	0.20
Meningitis, cerebrospinal (epidemic)	408	.39	7,118	0.01
Cerebrospinal fever	1,065	1.02	19,563	0.18
Chickenpox	618	.59	11,131	0.03
Typhoid fever	167	.16	10,001	0.01
	91	.09	2,756	0.007

TABLE III

Ten Leading Causes of Disability as Expressed by Numbers of Sick Days

Army	Sick Days ¹	Navy	Sick Days ²
Influenza	10,676,172	Influenza	1,366,625
Gonorrhea	3,903,303	Gonorrhea	647,326
Mumps	3,884,147	Mumps	630,126
Tuberculosis (lungs)	3,385,053	Tuberculosis	569,683
Bronchitis	3,287,643	Pneumonia (all)	509,259
Pneumonia (all)	3,079,023	Syphilis	398,858
Syphilis	1,927,901	Bronchitis	374,989
Measles	1,877,944	Measles	224,909
Dysentery (all)	1,060,229	Chancroid	202,304
Chancroid	973,614	Malaria (all)	103,257
Total	34,055,029	Total	5,027,336

¹ April 1, 1914 to December 31, 1918² Calendar years 1917, 1918 and 1919.

to epidemic conditions incident to outbreaks of a highly virulent form of influenza among troops in transit. As a rule, the epidemic attack rate on board ship was comparatively low, 16.3 per cent for battleships, 26.2 per cent for submarines and destroyers, and 8.8 per cent for transports. The epidemic death rate on battleships was 7.3 per 1,000, on submarines and destroyers 7.9 per 1,000, and on transports 2.2 per 1,000.

There were, however, notable exceptions such as the U. S. S. *Pittsburgh*, which encountered the disease in Rio de Janeiro and had approximately 80 per cent of its personnel affected. The U. S. S. *Yacona* furnished another exception with approximately 80 per cent of its personnel attacked. The origin of the epidemic of influenza on board the U. S. S. *Yacona* was New London, Connecticut.

A partial explanation of the variation in the rates for influenza afloat and ashore is that the Fleet is largely protected by a quarantine of recruits for about eight weeks at a Naval Training Station before the men are transferred to sea. The Naval Training Stations are also more exposed to infection from contact with civilians, which invites epidemic invasion.

TABLE IV

Ten Leading Causes of Death, United States Army Death Rates per 1,000

1917		1918		1919	
Measles	1.44	Influenza (all)	9.14	Influenza (all)	1.76
Lobar pneumonia	1.20	Lobar pneumonia	3.34	Tuberculosis (all forms)	1.50
Meningitis (epidemic)	.50	Bronchopneumonia	2.71	Bronchopneumonia	1.37
Bronchopneumonia	.36	Measles	.59	Lobar pneumonia	1.02
Crushing	.22	Meningitis (epidemic)	.47	Meningitis (epidemic)	.34
Suicide	.21	Tuberculosis (all forms)	.38	Fracture, compound	.21
Tuberculosis (all forms)	.20	Pneumonia, unclassified	.18	Fracture, simple	.18
Drowning	.15	Crushing	.18	Crushing	.16
Appendicitis	.12	Bronchitis	.17	Suicide	.15
Fracture, simple	.09	Fracture, compound	.17	Appendicitis	.12

For the Navy as a whole, there were 102,847 sick days from scarlet fever and 75,522 sick days from diphtheria for the years 1917, 1918, and 1919. Navy ships may visit ports where health authorities have neglected widespread immunization and should serious overcrowding again become necessary, there is every reason to expect that this experience will be repeated.

Following a recent epidemic of diphtheria in Halifax an extensive survey revealed the fact that only one person in five was immune to the disease. Immunity was no higher in the military and naval forces in and about the city. Inquiry reveals that there is a general belief among health officials that most adults are immune. The incidence rate for diphtheria has been low in both Canada and the United States for several years, and the health authorities have not been much concerned over possible epidemics from this disease. It is reasonable to believe, however, that large numbers of men of military age in the United States are non-immunes. Fortunately, this disease can be quickly controlled by widespread immunization with diphtheria toxoid. This method of control will greatly reduce the carrier problem which prevailed in 1918.

The ten leading causes of morbidity and mortality for the U. S. Navy for the years 1917, 1918, and 1919 appear in tables 5 and 6.

It should be remembered that the preparation for defense or the waging of war has always been attended by an increase in the prevalence and often a shocking increase in the virulence of disease. This is brought about by the rapid spread of infection incident to conditions of mobilization and transport of combat troops from widely separated parts of the world. In the civil population of Europe, now subjected to all the hazards of war, fatigue, famine, lack of sanitation, and inadequate medical care are the detonators for explosive epidemics. Just when the epidemic explosion may be expected is a matter of grave concern to epidemiologists.

The late Hans Zinsser,² basing his reasoning on experiences in the mobilization camps in 1917, pointed out that outbreaks of epidemics are almost inevitable when large numbers of men from all over the country are brought together in camps under circumstances which call for arduous physical and disciplinary training. Much control over the epidemic intestinal diseases such as typhoid and dysentery can be exerted by suitable preventive measures, but the situation with regard to respiratory diseases is more difficult. In such conditions as measles and mumps neither prevention nor treatment can be much better controlled than formerly.

Zinsser was convinced that the unimpeded flare-up of infectious diseases among young military units is stimulated by two factors—the too rapid bringing together of large numbers of susceptible young men with large numbers of carriers of the various respiratory organisms and the quite natural but too energetic efforts to force military training and the physical hardening process at a pace too strenuous for the relatively soft recruit.

Military mobilization presents a challenge and an opportunity. Available epidemiologic information must be utilized in planning each step of the assembly and care of the new recruits. The behavior of epidemic disease under the different circumstances which develop must be carefully recorded and analyzed. Only by immediate concentration on these two objectives will it be possible to profit fully from the unique epidemiologic opportunity furnished by mobilization.³

Since the war of 1914–1918, there has been a general strengthening of many public health measures, such as child health, tuberculosis, and the control of communicable disease including venereal disease control programs. The major success of these efforts is based on reporting, yet the reporting of disease is so unsatisfactory in the civil communities that Dr. Gallup⁴ has seen fit to take a nation-wide poll on the extent of last winter's epidemic of colds and "flu" and concludes as follows: "The probable dimensions of the last winter's flu epidemic are indicated for the first time in a survey by the American Institute of Public Opinion. Questions put to a cross-section of several thousand men and women in all parts of the country—the results of which will be of particular interest to the medical profession—point to the following conclusions:

- " 1. That fully a fourth of the adult population suffered from flu or grippe during the last winter. When this figure is applied to the total adult population of more than 80 millions, the Institute survey indicates that at least 20 million adult Americans were affected between October and March
- " 2 This survey did not include persons under 21 years of age which would mean an additional 12 or 13 million cases, assuming the same rate of incidence as among the older people
- " 3 Inadequacy of the normal health records on the subject is indicated by the fact that only one person in three who reported having had the flu said he had called a physician. The remainder said they had doctored themselves—either because ' it wasn't serious enough to call a doctor ' or ' because we couldn't afford one ' "

This poll further reports " For the first time in United States history it has been possible to chart the extent of America's No. 1 health problem—colds and flu

" More than 50,000,000 adults suffered from colds. More than 20,000,000 were affected by flu. The reason, of course, is that most cases of flu—and the overwhelming majority of colds—are simply never reported to doctors and health authorities

" Here are findings from the Institute Survey which will give medical and health authorities some of the first evidence ever obtained on the incidence and cost of the two ailments throughout the 48 States. This means that more than 50,000,000 adults suffered loss of vitality, efficiency or working time because of colds in the last six months. Assuming the same rate of incidence among those under 21, the results point to a total of about 81,000,000 who were affected. The combined replies indicate a total for

Santo Domingo Due to the acquisition of the new Bases, there is excellent reason to predict an increase in the number of cases of malaria among the military forces. The reason for this apprehension is that malaria is endemic in some of the areas where the Bases are to be located and the native populations will be difficult to control.

Should this prediction fail, it will be due entirely to the fact that the Army and Navy medical forces and the health agencies have been able to accomplish a huge task of malaria control.

The importation of large numbers of troops and civilian workmen to these Bases presents a real problem now because malaria carriers may start an epidemic and thus delay the construction of the Bases and the training of the troops. Of civilian concern is the return of these troops and laborers to their home communities. There is the ever-present prospect that some of them may become carriers and serve as a focus of an epidemic of malaria in areas where malaria has not existed for many years. There is a real shortage of competent medical and engineering personnel to handle malaria control problems for the armed forces and an equally important shortage of experienced medical personnel to cope with a malaria epidemic in an area previously free from this disease. For several years malariologists have noted the occurrence of malaria in areas in the United States free of the disease and many have speculated on the possibility of a return of malaria to these areas.

It is advisable to redirect the teaching of malaria in the medical schools and to encourage the strengthening of the malaria control units in key localities to prevent unnecessary deaths from malaria. There is need for intensive research on a more simple but reliable method of diagnosis, such as a precipitin test or skin reaction. The armed forces need a vaccine against malaria or a reliable drug for prophylaxis. Little progress has been made in the chemotherapy of malaria since the introduction of atabrin.

YELLOW FEVER

Since one insect-borne disease has been mentioned it is advisable to invite attention to the fact that yellow fever cannot be dismissed from the problems which must be met. It is now known that the "jungle type" of yellow fever is endemic in certain tropical areas and that at least one important outbreak of the disease has occurred in the Anglo-Egyptian Sudan. Little official information is available on this epidemic.

Yellow fever has for several years been a matter of concern to the National and some State health organizations because of the increase in airplane travel and the possibility that either infected travellers or infected mosquitoes introduced into the United States might result in a very dangerous situation.

It is reassuring to know that a vaccine is now available which produces lasting immunity, that it is available in considerable quantities, and that facilities for its manufacture can be speedily expanded.

The Army and Navy are vaccinating both the military and civilian populations ordered to areas where yellow fever may be endemic.

VENEREAL DISEASES

Colonel Harrison's "Venereal disease nausea" aptly summarizes the attitude in the higher reaches and the cloistered sectors of far too much of the world's medical profession to a group of communicable diseases which have been prime wasters of military man power for centuries. This unfortunate attitude is apt to increase and will further delay the control of syphilis and gonorrhea. No group of people thinking of emergency service can overlook this vexatious question.

From whatever viewpoint considered, the venereal diseases present the largest problem in preventive medicine confronting the military surgeon. They surpass in magnitude and administrative significance all other communicable diseases and, to make a bad matter worse, the research funds devoted to the study of these diseases are pitifully small.

The U. S. armed forces in World War I lost 7,492,510 sick days, or the equivalent of nearly 20,600 men for a whole year. Expressed in terms of ship complement, there were enough days lost to man five aircraft carriers and nine World War destroyers.

It should be remembered that the Army and Navy reject for enlistment and for Navy industrial employment men suffering from venereal diseases. The subsequent damage comes from the civil populations and this and other official medical bodies can and should do much to reduce venereal diseases incidence in the civilian population. Just one measure—law enforcement—would go far to reduce military damage from venereal diseases.

Surgeon General Parran has performed a magnificent public service—ever, though he has annoyed many complacent medical men—by focusing attention on the severity of syphilis as a health problem and breeding down the profit rules, per centage, and dependence on sex of the problem.

Typhus is showing increased activity in eastern Europe,¹ Spain,⁵ and China. An increase of typhus was noted in 1939 and 1940 in parts of Turkey, Bulgaria, and Yugoslavia,⁷ and more recent unofficial information indicates that there is a sharp rise in Poland and parts of Russia. The disease has appeared in parts of Germany, where it has not been endemic, notably in East Prussia and Polish Silesia. There was a small epidemic in Mecklenburg in March 1940.

An outbreak of dysentery comparable with that of World War I was reported in the German Army during the Polish Campaign of 1939¹ and in the French prison camps in 1940.⁵

In 1939, out of a total of 15 countries in the War Zone, 7 showed some increase in typhoid fever, as did Australia, Japan, and the United States.¹ It is expected that typhoid fever will remain a relatively minor problem in the armed forces of the United States at home, but increasing vigilance is necessary in the newly acquired Bases and in military and industrial concentrations.

The movement of population which occurred in England when the War began in 1939 was the greatest since the time of the Great Plague of 1665, when London was emptied of about 2/3 of its population. The total evacuation is reported to be in excess of 1,270,000, including children, expectant mothers, and the blind and crippled.⁷ This changed environment was expected to result in an increased prevalence of the communicable diseases. Inadequate sanitation, heating, and ventilation, and overcrowding of the bomb shelters and temporary quarters complicated the health problem and were thought to invite the spread of certain diseases. Increased foci for tuberculosis resulted from the limitation in hospitalization of the tuberculous. An unusually severe winter, shortage of fuel, and the black-out conditions encouraged the spread of respiratory infections. These factors augmented the health hazards of war resulting from mobilization, air raids, changes in work hours and dietary habits, lack of sleep, nervous strain, and increased fatigue especially noted among the industrial workers.

Fortunately, there has not been the general increase in infectious diseases that was predicted at the beginning of the battle of Britain. The incidence of respiratory infections was somewhat higher than usual, but there was a significant reduction in the number of reported pneumonia deaths. This has been attributed to the use of sulfanilamide and related compounds.⁷

Both influenza and cerebrospinal meningitis have been widespread. Influenza is not a notifiable disease in England, hence the incidence record of this disease is in the same class as the American experience. The number of reported deaths from influenza up to March 1940 was higher than the expectancy for the season. Influenzal pneumonia is being reported.

Previous reporting of cerebrospinal fever in England and Wales has never approached the 1939-40 figures.¹ The unofficial reports for the first six weeks of 1941 indicate about the same degree of prevalence. Case fatal-

ity varies greatly in different parts of the country, but on the whole is much less than in 1914-18 when the fatality among civilians was about 60 per cent and in some localities as high as 80 per cent. Case fatality for the 1939-40²-41⁷ period is from 10 to 12 per cent. However, private reports indicate a mortality of 30 per cent from children groups in certain communities.

An Associated Press despatch dated January 7, 1941,⁸ quoted Sir William Jamison, Chief Medical Officer of the Health Ministry, as reporting increases of cerebrospinal meningitis, pneumonia, typhoid fever, and dysentery for England and Wales for the year 1940.

Conflicting opinions are encountered on the incidence of neuropsychiatric disorders and this uncertainty will probably remain until the official figures are released.

The latest published information from Great Britain (1940)¹ indicates that the health of the Army is good except for epidemics of German measles, influenza, and cerebrospinal fever. The occurrence of cerebrospinal fever was sporadic and showed a fatality rate markedly lower than for the War of 1914-18. Certain treatment centers are reporting an increase in venereal disease, but the prevalence in the defense forces is not considered comparable with the early stages of World War I.

WHAT SHOULD BE DONE

Due to the geographic location of the United States and the present focus of war, none of the organizations of the warring nations is quite applicable to the American form of government or to the mental attitude of our people. Large areas of this country obviously need no protection, either because they contain no vital industrial facilities or they are so sparsely populated that no foreign power would waste aircraft and other costly weapons upon them. However, almost every large community has vital activities, such as industrial establishments, transportation centers, and administrative offices, and they would be considered worth the attention of the parachutist, alien saboteur, or a few bombs. In each of these localities effective organization of both protective and medical facilities is necessary, not only to save life but for the effect on national morale.

The fullest possible use should be made of existing local, state and national official organizations, such as the Red Cross, Boy Scouts, American Legion, etc. The police and fire departments should be the nucleus of the local civilian organization.

Suggested Organization for the City or Local Government

- (1) The evacuation
- (2) Transportation, ambulances, private cars, boats, drivers
- (3) Public utilities. Security, maintenance, and repair of power system. Water and sewage systems, gas and telephone systems
- (4) Regional food depots

- (5) Bomb-proof shelters
- (6) Casualty services
 - (a) First-aid posts
 - (b) Hospitals The expansion of existing hospitals The construction of new facilities
 - (c) Shock and hemorrhage service Plasma production
- (7) Special services
 - (a) Communications
 - (b) Reporting Liaison
- (8) Fire
 - (a) From incendiary bombs
 - (b) Ordinary fire protection
- (9) Police
 - (a) Ordinary law enforcement
 - (b) Specially trained persons for the detection of saboteurs
- (10) Sanitation
 - (a) Usual supervision
 - (b) Decontamination of gassed areas
- (11) Disaster relief
 - (a) Emergency care of wounded
 - (b) Care of the dead
 - (c) Rescue
 - (d) Demolition of unsafe structures
 - (e) Road clearance and maintenance
- (12) Personnel
 - (a) Physicians, nurses, dentists, stretcher bearers, laboratory and other technicians, orderlies, and clerks
- (13) Equipment and supplies

The details of the local functions are obvious and need no further elaboration, but organization should be such as to meet the anticipated needs of the local situation

Suggested Organization for the State Government

- (1) The transportation and care of the chronically ill, hospital populations, and all evacuees
- (2) A greatly augmented statistical service for the handling of morbidity and mortality statistics (these data should be current and receive wide administrative distribution)

- (3) The rapid evacuation of civilians whose occupations are not essential to the efficient operation of the country should an air attack warning be received is one of the obvious services to be rendered in order that the maximum use might be made of hospitals and medical services for possible wounded. This would include the children, the old, the infirm, and expectant mothers

WHAT HAS BEEN DONE

Almost a year ago, April 26, 1940, the Surgeons General of the Army and Navy invited the Division of Medical Sciences of the National Research Council to "stand by" to assist the Armed Services in preparing for the emergency.⁹ About the middle of May, 1940 the Surgeons General of the Army and Navy requested Dr. Lewis H. Weed, Chairman of the Division of Medical Sciences, National Research Council to establish special committees to act in an advisory capacity to the two Armed Services. At the early meetings of these committees, many problems relating to other branches of medicine and pertinent to military affairs were presented and it was quickly realized that it would be necessary to appoint committees to explore the whole field of medicine. In all, seven main committees have been appointed, under which 34 sub-committees are operating.

The meetings of these committees are attended by liaison officers from the several military and civil agencies requiring their services. These committees have accomplished a splendid service, including the preparation of many Manuals and recommendations, and the service will be expanded with the acquisition of additional funds.

The American Medical Association has undertaken the huge task of determining the number of physicians available for service, the codification and classification of their special training, and other pertinent data.

The Health and Medical Committee was established by Order of the Council of National Defense dated September 19, 1940. The Order reads "It will be the responsibility of the Committee to advise the Council of National Defense regarding the health and medical aspects of National Defense and to coordinate health and medical activities affecting National Defense." This Committee was transferred to the Federal Security Agency on November 28, 1940. The order of transfer stated, "such committee shall hereafter exercise its duties and functions under the direction and supervision of the Federal Security Administration." This Committee has appointed six sub-committees, one of the most important of which is the Subcommittee on Industrial Health and Medicine. The deliberations of this Subcommittee have produced recommendations which will result in the improvement of industrial health practices and reduce illness from manufacturing processes.

The Navy is engaged in an intensive program of training medical officers in industrial hygiene and industrial medicine. When their training is com-

plete it is planned to set up an Industrial Hygiene and Industrial Medicine unit in each Naval District, to investigate industrial health conditions, submit recommendations, and, when approved, supervise the installation of improvements to reduce the health and accident hazards in Naval industrial establishments

The Army has established a Board for the investigation of influenza and other epidemic diseases. This Board is composed of Drs Blake, Pepper, Warren, Doshez, Avery, Maxcy, and Goodpasture. Its function is to plan and recommend policy for the investigation of epidemic diseases. Under the Board there are Commissions on the following diseases

- (1) Epidemiological Survey, Chairman, Dr Stanhope Bayne-Jones, Yale University
- (2) Measles, Chairman, Dr Joseph Stokes, University of Pennsylvania
- (3) Meningitis, Chairman, Dr Perrin H Long, Johns Hopkins University
- (4) Pneumonia, Chairman (has not been appointed)
- (5) Neurotrophic virus disease, Chairman, Dr John Paul, Yale University
- (6) Hemolytic streptococcus infections, Chairman, Dr Martin H Dawson, Columbia University
- (7) Influenza, Chairman, Dr Thomas Francis, Jr, New York University

These Commissions are organized for active field duty in case of need

The Navy is organizing epidemiological teams to work with the Division of Preventive Medicine, Bureau of Medicine and Surgery, and their function will be similar to that described for the Army

The American Red Cross is cooperating with the Subcommittee on Blood Substitutes, of the National Research Council, to procure blood donors and to arrange for the manufacture of a supply of dried and liquid plasma for the Armed Services

The Rockefeller Foundation has manufactured and has in store a supply of yellow fever vaccine for the use of the Army and Navy. In addition, the International Health Division of the Rockefeller Foundation, under the able leadership of Dr W A Sawyer, has agreed to cooperate with the Army and Navy in sanitating the extra-cantonment areas of the newly acquired Bases and in such other advisory service as may be necessary and required

PHYSICIANS FOR BRITAIN

Great Britain's appeal for physicians through its National Red Cross has received the official approval of both the President and The Secretary of War in the following press releases, April 21, 1941.

"The British Red Cross has appealed through the American Red Cross for at least 1,000 young American doctors to help it meet an acute shortage of doctors in

British military and civilian hospitals As President of the American Red Cross I heartily approve this request

"When the British appeal came to my attention, I asked the opinions of the Surgeons General of the Army, Navy and Public Health Service They join me in believing we should encourage eligible American doctors to volunteer for this humanitarian service with our British friends I also am informed that the Division of Medical Sciences of the National Research Council, the American Medical Association, the American College of Surgeons and the American College of Physicians have offered their assistance to the American Red Cross in meeting this emergency

"The young doctors whom Great Britain so desperately needs can do much to heal the wounds inflicted alike upon civilians and military in this cruel war Those who volunteer will be enrolled by the British Red Cross and will work under the protection of the Red Cross Treaty of Geneva, a covenant which has been respected by belligerents since 1864

"To any American doctor, who is eligible and able to go, service in this cause presents a splendid opportunity"

/s/ FRANKLIN D ROOSEVELT

"In connection with the appeal of the British Red Cross to the American Red Cross for the assistance of at least 1,000 American Doctors, the question arises Can we spare the men?"

"Naturally we must look to our own interests in the light of the emergency which faces the world today We shall need several thousand more doctors in our own Army However, I feel that we should do all in our power to aid in obtaining these physicians, consistent with the needs of our own medical defense I can see no objections, therefore, to the fulfillment of this request through the machinery of the American Red Cross

"Doctors who volunteer would serve under the terms of the Red Cross Treaty of Geneva, a convention 77 years old and guaranteeing immunity of medical workers on the field of battle Both Allied and Axis forces are signatory to this treaty To my knowledge, the principles of this agreement never have been violated

"I am in personal sympathy with the proposal that we provide Britain with doctors If the British need doctors—and we know that they do—I believe we can and should provide them with some of ours"

/s/ HENRY L STIMSON

The urgent appeal for at least 1,000 physicians to augment the British Medical Services is a need of prime importance Due to the exigencies of the service it is desired that these men be under 40 years of age, unmarried, and eligible for entry into the armed services of the United States They will not be expected to swear allegiance to Great Britain, but will serve the military services and civilian population both in England and the Empire Their compensation will be comparable with that of a First Lieutenant in the U S Army They will be licensed to practice in the Empire during their service and will be eligible for promotion, gratuities, and pensions

Then physical, professional, and moral qualifications will be carefully judged by the Medical Sciences Division of the National Research Council, assisted by representatives of the American Medical Association, American College of Surgeons, American College of Physicians, and the American Red Cross They will be certified for passport visa and their travel expense paid by Great Britain

The question naturally arises "How many physicians of the age group and qualifications are available?" It has been estimated that there are fewer than 10,000 such men in the medical profession of the United States.

This appeal for medical assistance places squarely before this and other medical organizations a task that may require a revision of the medical, hospital, and teaching organizations of the whole country

The writer desires to express his gratitude to Mrs Laura T Anderson, Senior Clerk, Bureau of Medicine and Surgery, Navy Department, for her editorial assistance in the preparation of this paper, and to Lieutenant (jg) George W Mast (MC), U S Navy, and G B Peterson, Pharmacist's Mate, 1cl, U S Navy, for their assistance in searching official records

The opinions or assertions contained herein are the private ones of the writer and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large

BIBLIOGRAPHY

- 1 COLVETL, CLARA E Pub Health Rep, 1941, 141, 572
- 2 ZINSER, HANS On the medical control of mobilization, The Mil Surgeon, 1940, 144, 214
- 3 Jr Am Med Assoc, 1940
- 4 The Gallup Poll, Washington Post, April 12, 1941, p 9, and April 13, 1941, Section 11B, p 1
- 5 SAWYER, W A International Health Division, Rockefeller Foundation, personal communication
- 6 PEREZ, J A (MC), U S Navy, personal communication
- 7 NORMAN, I L (MC), U S Navy, personal communication
- 8 New York Times, January 8, 1941, p 3
- 9 LARKEY, S V War medicine, 1940, 1, 77

THE RECRUIT'S FIRST YEAR *

By P S MADIGAN, F A C P , *Medical Corps, U S Army,*
Washington, D C

SINCE the birth of our nation and the formation of a defensive army to protect our shores, it has forever been foremost in the minds of our military leaders to stress the point that the art of soldiering should be a vocation of life. Every vocation of necessity has its prerequisites, and the art of soldiering differs in no way from this general principle. Numerous writers throughout the history of our country have dilated upon this aspect in their description of military life.

During the present emergency it is incumbent upon the Army to train a million and a half soldiers. We must give these young men the best of care and treatment from all angles possible.

There are certain angles of military life that I wish to call to your attention that are of extreme importance. The foremost of these is that of military discipline. This subject is one but little understood outside of the Army and, it must be confessed, is not always viewed in its proper light even within the Army. It has been said that the trouble seems to be that most people either do not, or will not, grasp the proper meaning of what is called military discipline, its nature, its purpose, its necessity, and finally and most important of all, its spirit.

Living within an atmosphere of strict discipline from the cradle to the grave, most people fail to grasp its primary principles. As a matter of fact, the idea of rigid discipline surrounds us every moment of our lives. We can never escape it for an instant. Practically every experience through which we acquire knowledge is in the nature of a disciplinary correction inflicted upon us by some agency of nature or of civilization.

Outside of military circles the average man recognizes fully the necessity of discipline in his family, his business, his relations with his fellowmen, because he is familiar with the conditions which surround the rearing of a family or which must govern the relations of men in civilized intercourse.

On the other hand, he is not familiar with conditions in the military service, hence, he does not understand the reasons for the rules and regulations, and in consequence is more than likely to view them with intolerance. Even within military circles, among men who should be familiar with the reason and spirit of military regulations and military procedure, many make the serious mistake of confusing the exercise of authority with the maintenance of discipline. In brief, they appear to think that discipline must be maintained solely for the purpose of upholding their authority, and again, both outside and inside of military circles, many fail to understand the

* Read at the Symposium of Military Medicine, Boston meeting of the American College of Physicians, April 24, 1941

spirit upon which true military discipline is based and must be based. Failing in this, they fail altogether, for the simple reason that men can understand the principle of military discipline only when they appreciate its underlying spirit.

Without the proper spirit there can be no such thing as discipline in any army. Proper discipline should in no sense be based upon the fear of disciplinary correction, since in this instance we merely have school-room discipline. The discipline upon which a successful army must be built is a different kind,—a kind that endures when every semblance of authority has vanished, when the leader has fallen, when members of the team are dropping out one by one and when the only driving power that remains is a strong and unconquerable spirit of attainment. *This concept gives us at once a working definition of military discipline, the spirit of the team.*

Strange as it may seem, an element of good discipline is the fear of losing the respect of one's fellow soldiers or officers, and this desire for esteem is one of the essentials of military discipline. It is to be seen in all trained and disciplined units the members of which feel for each other a natural respect and admiration. The knowledge that he enjoys the respect and admiration of his fellow soldiers is a source of the greatest pride to each member of the unit. The desire to retain this respect, to be looked upon as a worthy member of the unit, is greater than a man's fear of injury.

Oftentimes the question may be asked, "Of what necessity is military discipline?" I can only refer you to the necessity of team work in any undertaking, irrespective of whether it be team work in a set of doubles at tennis or the training of an Army of a million and a half soldiers.

In our present emergency we are attempting to inculcate in the minds of our soldiers the necessity of properly protecting our country in the event of attack. As Major General William A. Pew, Massachusetts National Guard, states in his manual, *Making a Soldier*, the kind of soldier who interests us is the one who finds satisfaction in serving a cause and who has learned to expend his energy for that cause. He must be physically developed, trained to conserve health, and he must perform with technical skill his part in every incident.

Besides these qualifications he must have the mental attitude of a soldier. To attain this proper attitude is an important step, there is an ideal which is characterized by the tendency to correct action and supreme satisfaction in such action.

In this short treatise, considerable stress is placed upon the process of acquiring proper military habits and the author gives four maxims:

1. Select the habit
2. Demonstrate the habit
3. Secure abundant and genuine practice, with every effort of will and attention directed toward acquiring the habit
4. Allow no exceptions

Under this grouping this author classifies military bearing, courtesy, putting forth physical and mental efforts (that is, high level of efforts), self control (physical and mental), neatness and order, smartness, exactness, and promptness, sub-conscious obedience, mental alertness, and confidence, and last but not least, team work in all military efforts

In order to procure the best possible selectees to conform to the standards laid down by the Army, the Surgeon General's Office, in conjunction with the Selective Service System, has issued circular letters containing instructions to neuropsychiatrists examining selectees and recruits for the Service. In these circular letters the idea is again stressed that Army life is to be looked upon as a vocation and that certain types of individuals are adapted to this vocation and others are not.

No applicant is rejected unless we have definite neuropsychiatric evidence that he will be unsuitable material for training in the Army. It is further stressed that the soldier must be looked upon as a fighting unit, capable of adapting himself to the restrictions and inhibitions of personal desire and comfort, as well as to the deprivation of food, rest, shelter, and as occasion arises, to the extraordinary demands of prolonged physical and mental activity during active military service.

It has been further stressed that there are many individuals of abnormal personality traits who are capable of satisfactory adult adjustment in civilian life. For this class there are in civilian life numerous avenues of escape available, but such individuals will be a total loss when it comes to adjusting themselves to a pattern which is more or less inflexible and of necessity limited and circumscribed as to self-expression. When thrown upon their own meager resources of adaptation to Army environment, requiring contact with all kinds of personalities, some who are just able to adapt themselves to life under the most favorable conditions will not fit into that one iron mold which experience has taught is essential to military success.

Applicants who exhibit definite personality deviations are referred for special psychiatric survey and are rejected if they are considered as undesirable material for training. It is estimated that over 50 per cent of the present beneficiaries of the Veterans Bureau are individuals of this type who were accepted in the Army in 1917.

The Army is one of the elements of national defense, and its present mission is one of preparation for offensive and defensive warfare. It is, in no sense, a social service or a curative agency. It is to be considered neither a haven of rest for the wanderer or shiftless, nor a corrective school for the misfits, the ne'er-do-wells, the feeble-minded, or the chronic offender. Furthermore, it is neither a gymnasium for the training and development of the undernourished or underdeveloped, nor is it a psychiatric clinic for the proper adjustment of adults who need emotional development. Therefore, there is no place within the Army for the physical or mental weakling, the potential or present behavior problem. If an individual is a behavior problem in the

civilian community, he will certainly become a more intensified problem in the Service

In our present training schedule, it must be forever kept before our minds that our soldiers are coming from all walks of life, from distant points of the country, from farm and factory, from ranch and bench,—the rich and the poor, the illiterate and the educated,—and all are thrown together into a heterogeneous mixture and subjected to the same discipline, the same regulations the same dull routine

The selectee coming from the average American home has received the fond care and protection of indulgent parents. He has been protected from all disturbing and disrupting influences that might interfere with his normal development. His parents have been interested to see that he had the proper clothing for all types of weather, that he did not leave the house without his overcoat, overshoes, muffler, or whatnot in inclement weather. New problems that confronted this individual were promptly taken over by his protectors and solved by them.

In other words, his entire life has been guarded and protected, and his course of action steered by over-seeing parents. His personal responsibilities have been at a minimum, and he has not been trained to accept life as it really is.

Upon this boy's induction into the Army, you will readily see that a tremendous amount of psychological readjustment must be made. Here he must train himself to stand upon his own feet, to make decisions, learn to live with other men, adapt his own personal wishes to the wishes of others about him. He must live in close contact with his fellow soldiers and adjust himself to their method of living.

In other words, he is passing from a set of circumstances where the stage was set about him and his wishes, to one where he must recognize, appreciate, and conform to the personal desires and wishes of his fellow soldiers.

This readjustment will have a wonderful effect upon the boy's future. During the recruit's first year of service, he will experience a well-planned period of training to develop his professional abilities as a soldier, as well as to develop his character.

After the selectee has been chosen, ordinarily he will be sent to one of our training areas for a period of 13 weeks' training. In the case of the Medical Department, the instruction day is assumed to be eight hours, more time per day being utilized when desirable, especially in connection with marches, field exercises, and the like. The open time will be used to compensate for interruptions, to bring units or individuals up to standard, or to provide refresher training.

During the first two weeks, the training of the enlisted man will be stressed. At the end of this period, he should be able to wear, display, and properly care for his uniform and equipment, to march, to pitch shelter tent, and to understand the essentials of the basic subjects prescribed in this program, such as

- Military courtesy and discipline
- Military sanitation and first aid
- Care of clothing and equipment
- Individual defense against chemical warfare
- Individual defense against air and mechanized attack
- Interior guard and close order drills
- Equipment, clothing, and tent pitching
- Marches and bivouacs
- Physical training, group games and mass athletics

During the second period of training, from the third to the tenth week inclusive, stress is placed upon basic technical subjects which fit him for his place in the unit

In addition to the basic subjects, specialized training and technical and logistical training are started

TECHNICAL

- Hasty entrenchments and shelter (camouflage)
- Drill, motor carriers, and motor units
- Motor vehicles, care, operation, and convoy
- Map and aerial photograph reading
- Movement by motor entrucking and detrucking
- Movement by rail, entraining, and detraining
- Loading and handling cargo

MEDICAL DEPARTMENT TRAINING

- Elementary anatomy and physiology
- Nomenclature and care of organization equipment
- Field medical records
- Treatment of gas casualties
- Litter drill, including ambulance loading and unloading, and passage of obstacles
- Field sanitation and sanitary appliances
- Materia medica and pharmacy
- Medical and surgical nursing
- Heavy tent pitching
- Organization and function of the arms
- Organization and function of the medical unit
- Medical aid (splints and splinting, bandages and dressings)

TACTICAL AND LOGISTICAL

- Scouting and patrolling, use of cover and concealment
- Orientation in night combat
- Communications in combat

- Unit training (medical units)
- Battalion tactical training
- Regimental tactical training
- Troop movements by motors
- Inspections

The final period, from the tenth to the thirteenth week, inclusive, is known as the tactical period

- Function and combat dispositions of sections of headquarters and service, collecting ambulance, or clearing elements
- Reconnaissance, use of cover and concealment
- Collection and evacuation of casualties from the field (day and night)
- Ambulance driving shuttle (day and night)
- Ambulance driving convoy (day and night)
- Nursing and ward management
- Transportation and supply requirements
- Procurement and issue of supplies
- Selection and occupation of various station sites, and the functioning of such stations
- Forward displacements and withdrawals during action
- Operation of regimental and battalion dispensaries
- Battalion or regiment training

It is astonishing how well and how rapidly recruits adapt themselves under these most difficult conditions. It is the duty of every officer to forever keep these conditions in the foreground and to lend every opportunity to advise and counsel with the men placed beneath him for proper training in military life.

Every effort has been made by the War Department to take proper care of the soldier from a medical and physical standpoint. The daily duties are properly coordinated to give him sufficient periods of rest and relaxation, he will be kept busy in mastering the new technic of his vocation. The activities of the various welfare associations have been adequately correlated and will be used to their fullest extent. A distinct effort has been made by the War Department to place the new soldier in the position for which he is best fitted, and every soldier is interviewed with this end in mind upon his entrance into the Service.

Recruits are encouraged to keep in contact with their family and friends by personal correspondence and by personal visits, they are given ample permission to leave the post in order to visit home and relatives when it does not interfere with their proper training schedule.

The entire program aims at producing an efficient, well-disciplined, high-morale Army that will satisfactorily protect our country in the event of necessity.

As one of our officers has expressed in his writings, the foundation stone of Americanism is uniform justice to all. This is what the enlisted man expects and this is what appeals to all. He is the finest soldier in the world, it is a great privilege to train him. Remember, he often comes from a home where there were few advantages and opportunities. Don't expect too much of him at first. He presents himself to be shown, to be instructed, to be molded properly, into this Army of ours. Have patience with him. Remember that many things which are an old story to us are new to him. Show him a thing clearly before you question him about it. If you are fair and square and interested in the general welfare of your men, you will appeal to them and they will follow your guidance willingly.

BIBLIOGRAPHY

- REYNOLDS, ALFRED The Life of an Enlisted Soldier in the United States Army, 1904
 PEW, W A Making a Soldier, Massachusetts National Guard, 1917
 HARBORD, J G The Officer's Guide, Produced for the Infantry, 1930
 MOSLEY, VAN HORN Suggestions from a General to the Youngsters of His Command, January, 1933
 Circular Letter No 19, Surgeon General's Office, March 12, 1941
 Medical Department, U S A, Training Program for 1940

SILENT OR ATYPICAL CORONARY OCCLUSION

By WILLIAM D. STROUD, M.D., F.A.C.P., and JOSEPH A. WAGNER, M.D.,
Philadelphia, Pennsylvania

RECENT papers by Blumgart, et al.¹ - wherein careful correlation between clinical records and exacting pathological studies were carried out, have again drawn our attention to the extensive potential collateral circulation that exists in the myocardium and secondly to the fact that, "coronary occlusion, *per se*, does not necessarily produce any characteristic clinical manifestations" "If an occlusion occurs gradually, with concomitant development of an anastomotic circulation, no symptoms or signs will be produced and no myocardial lesions will be demonstrable. Then what we speak of as 'coronary occlusion' which consists of substernal pain and oppression, a fall in blood pressure, pallor and typical electrocardiographic changes, fever, leukocytosis, etc. is in reality myocardial infarction."

TABLE I
A Few of the Many Clinico-Pathological Reports on Coronary Occlusion

	No. of Cases	Per Cent Without Pain
Morawitz and Hochrein ¹⁰	91	75.0
Willius and Brown ¹¹	86	25.0
Nathanson ¹²	113	20.0
Pollard and Harvill ¹³	375	8.5
Kennedy ¹⁴	96 (recent)	8.3
	102 (old)	36.3
Boyd and Werblow ⁷	127	33.0
Gorham and Martin ¹⁵	100	42.0
Stroud and Wagner	49	26.5

Many cardiologists have been conscious of this differentiation for some time. Smith³ writes, "complete occlusion may not be suspected during life" and that there may be "sclerosis of coronary arteries out of all proportion to clinical manifestations." Levy⁴ who developed the "Anoxemia Test" for the detection of coronary artery disease recognized that "advanced disease of coronary arteries may be found at necropsy in persons who, during life, never experienced discomfort referable to the heart." It appears as a result of the writings of these authorities and others that "silent" coronary occlusion is a clinical and pathological fact. The explanation offered is that sufficient collateral circulation has developed to prevent acute anoxia and ultimate necrosis of localized areas of myocardium.

* Read at the Boston meeting of the American College of Physicians, April 22, 1941.

This work has been done through the Robinette Foundation of the University of Pennsylvania and the M. W. Stroud, Jr. Fellowship in Cardiology of the Pennsylvania Hospital.

Does "silent" or painless myocardial infarction occur? White⁵ states that "if coronary obstruction and cardiac infarction develop slowly and there is no excessive cardiac strain, there may be no symptoms at all even though there be extensive areas of damaged muscle and even if one or both coronary arteries have been occluded" East, et al,⁶ Boyd and Werblow,⁷ Wedd⁸ and Wigser⁹ have described cases of proved myocardial infarction whose only complaints were sudden dyspnea and progressive failure

The literature includes many reports on the correlation of clinical and pathological findings in cases of coronary artery disease The incidence of painless occlusion in these series appears quite high

Unfortunately it is impossible in some of these reports to discern what is the exact pathology described, i e, coronary sclerosis with narrowing of the lumen, coronary thrombosis with or without myocardial infarction or if infarction is present, whether or not it is old or recent Further, unless very careful pathological examination is made by a pathologist especially trained

TABLE II
Acute Myocardial Infarction Without Pain

	Cases	Symptoms
Hypertensive	2	Vertigo and syncope
Arteriosclerotic with mild failure	7	Sudden increasing dyspnea and failure
No cardiac history	4	Sudden dyspnea, with pulmonary edema in one case

in cardiac pathology, it is very possible that a goodly number of coronary occlusions together with small myocardial infarcts would pass undetected

Looking at the clinical side from a critical standpoint, one is concerned with the questions, who took the histories, with how much care and how completely are they recorded? By some, the vague discomforts described would be ignored and yet by others, especially trained, interpreted as typical angina pectoris Often the patients are too sick to permit an exhaustive history and sometimes too deeply narcotized, especially postoperatively, to present a reliable record

A review of our cases of acute myocardial infarction as proved by progressive serial electrocardiographic changes or by necropsy examination at the Pennsylvania and Bryn Mawr Hospitals for a limited period of time was undertaken Cases suggestive but not proved by the above methods of examination were not included It is to be remembered, however, that there are certain areas of cardiac infarction, especially along the lateral wall of the left ventricle, that are relatively "silent" so far as the electrocardiogram is concerned Patterns for this area have recently been described A resumé of our cases of painless myocardial infarction is summarized in table 2

A few of the more typical cases are briefly described and their respective electrocardiograms presented

CASE REPORTS

Case 1 U. A., white female aged 49 years. No history of previous illness except slight dyspnea for three months. The patient was admitted to the hospital with a chief complaint of severe dyspnea with onset 48 hours previously. Examination revealed no pain, substernal or elsewhere but the patient was acutely ill with râles at both bases of the lungs and a blood pressure of systolic 170, diastolic 100. Gallop rhythm was present. A blood count revealed white blood cells 26,300. The following day her right foot became blue and cold with the pulses absent. Serial electrocardiograms showed a typical anterior infarct which permitted the diagnosis of mural thrombus with embolism to the right popliteal artery. Death ensued.

U.A. #15482 8/4/36

#15502 8/11/36

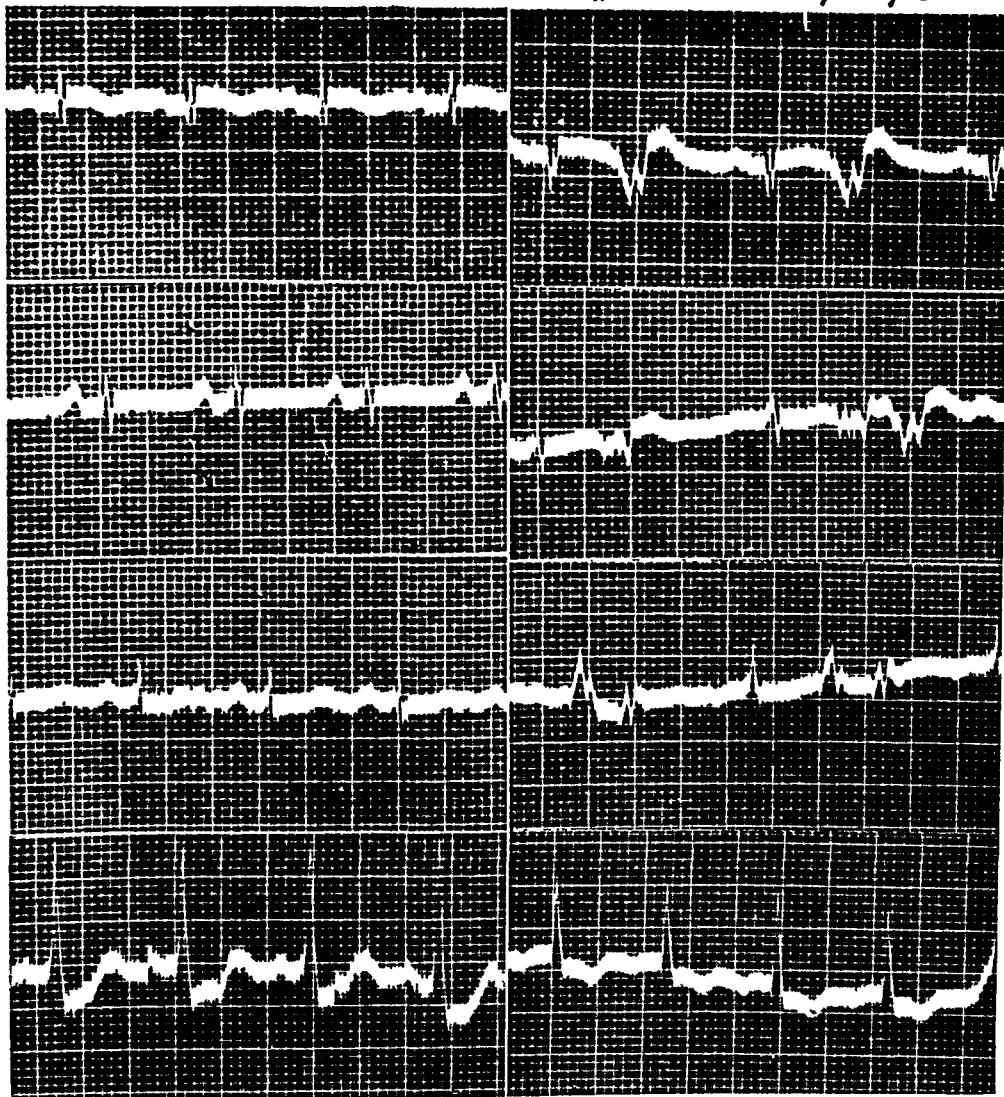


FIG 1 U. A. Electrocardiograms of Aug 4, 1936. Typical RST changes of acute infarction involving the anterior wall. Electrocardiograms of Aug 11, 1936 show further changes confirming this condition.

Case 2 J F B , white male, aged 76 years, was known to have hypertension (blood pressure systolic 170, diastolic 110) and arteriosclerotic heart disease requiring digitalis On March 23, 1941 the patient had much " gas " and belching but no pain This continued through the night and the next day examination revealed a blood pressure of systolic 130, diastolic 82, temperature 100° F , pulse 60 , possibly slight congestive failure present On March 25, 1941 a loud friction rub medial to the apex was audible The white cell count was 18,300 Electrocardiograms showed an acute posterior myocardial infarct Death ensued

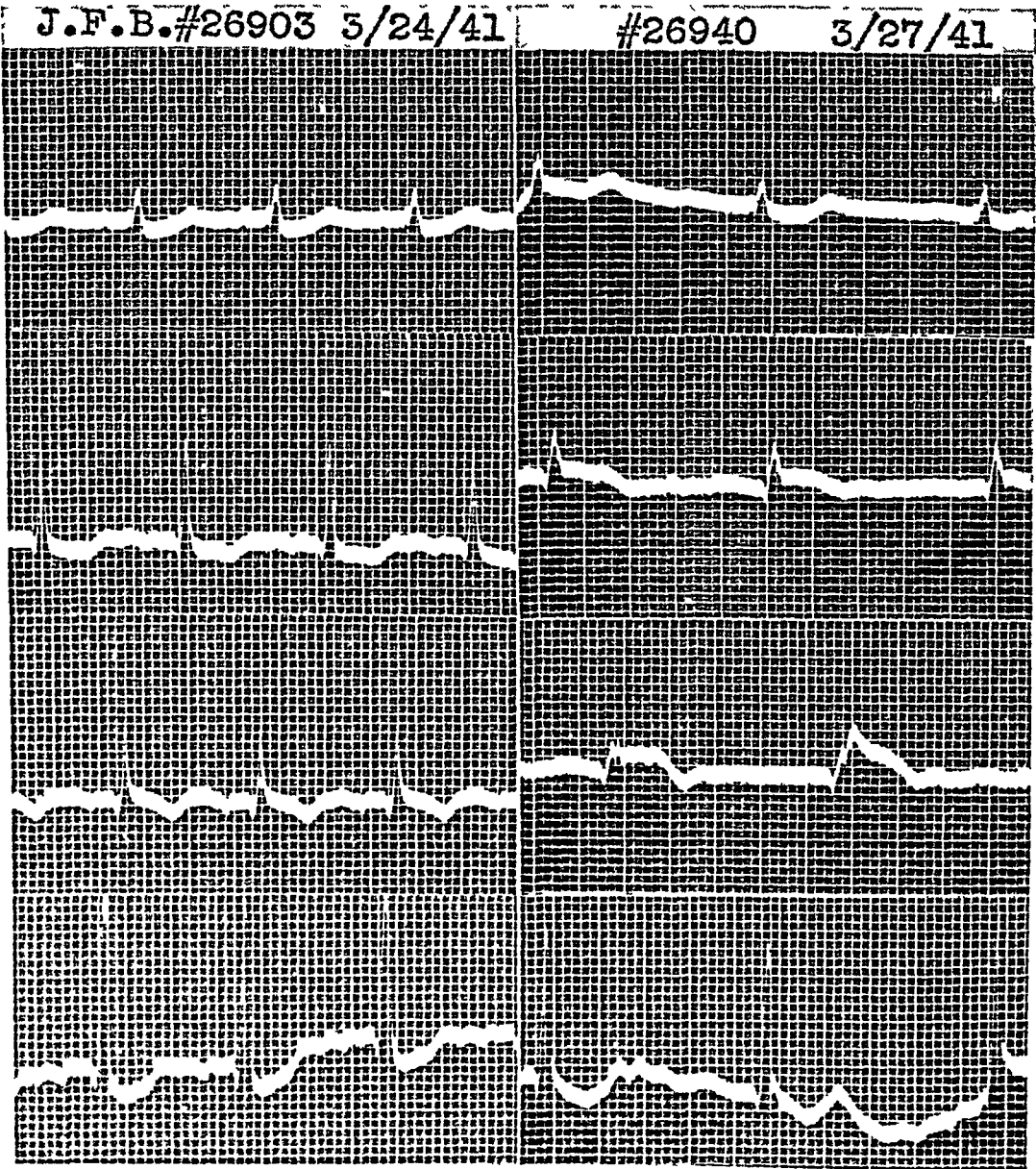


FIG 2 J F B Electrocardiograms of March 24, 1941 suggestive but not conclusive evidence of acute infarction of posterior wall Electrocardiograms of March 27, 1941 show further evidence in support of this condition

Case 3 H T, white male, aged 51 years, with a history of hypertension. He collapsed on the street because of severe dyspnea but had no pain of any description. The patient was exceedingly orthopneic and pulmonary edema was present. Examination revealed that his heart was enlarged to the left with a ventricular rate of 120 and normal sinus rhythm, blood pressure systolic 130, diastolic 90, white blood cells 17,500. The diagnosis was left ventricular failure. Serial electrocardiograms showed a myocardial infarction.

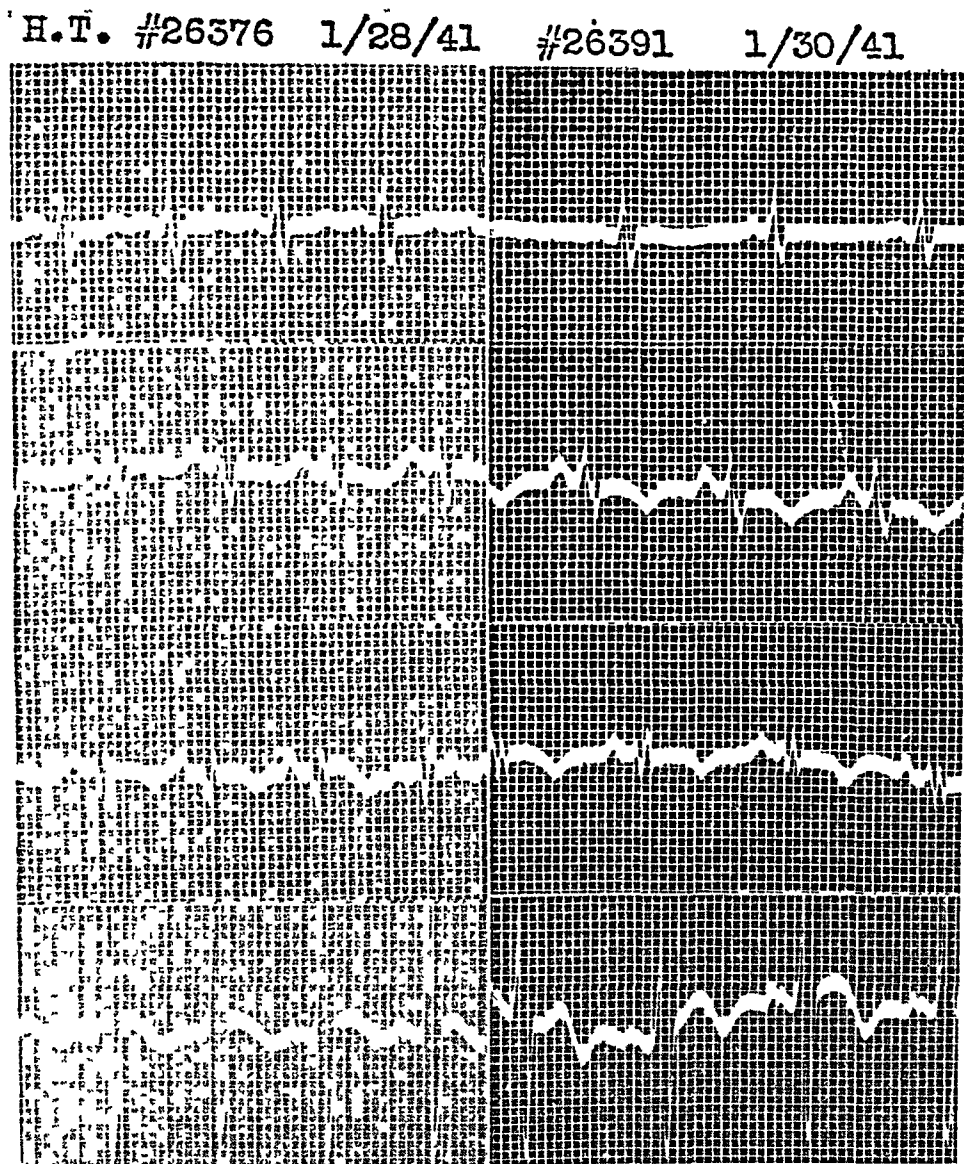


FIG 3 H T Electrocardiograms of Jan 28, 1941. Changes suggestive of myocardial infarction. Electrocardiograms of Jan 30, 1941, show progressive changes which further confirm the original impression.

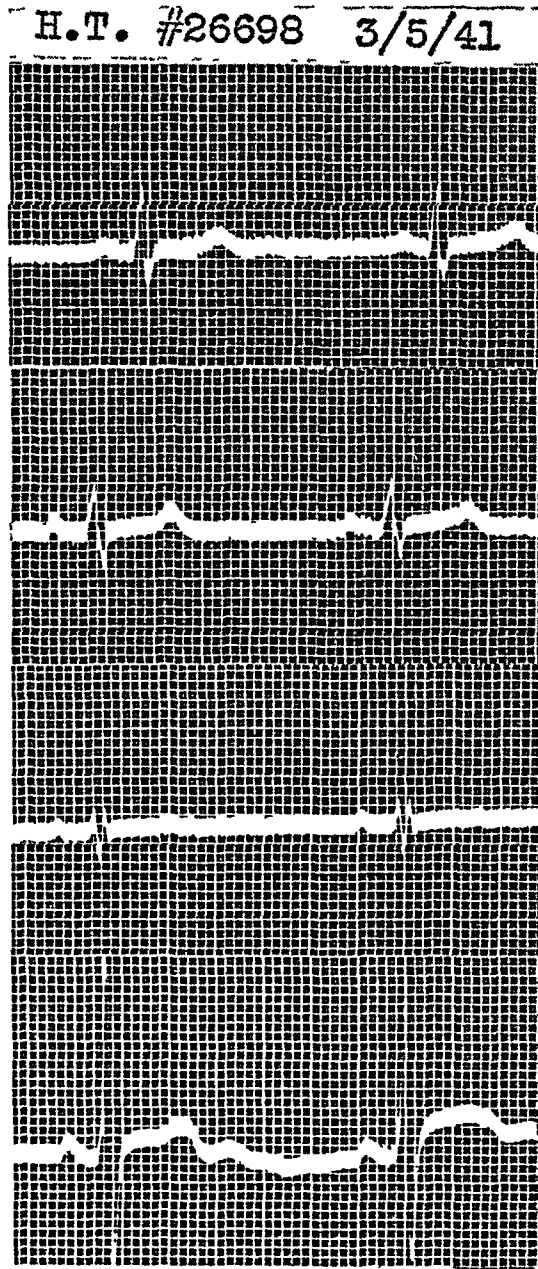


FIG 4 II 1 Electrocardiograms of March 5, 1941 show further evidence of change, now nearly normal

COMMENT

It is interesting to speculate on how painless coronary occlusion and painless myocardial infarction do occur. Most of us believe with Levy⁴ and others that heart pain is the result of myocardial anoxia no matter how brought about. Coronary occlusion, we say, can be painless because of an established compensated collateral circulation, but this is not the case in myocardial infarction.

The explanation of painless infarction is difficult. Possibly the symptoms which they experience, such as swallowing, choking, gagging or dyspnea

may be pain equivalents. Possibly the nerve supply about the coronary vessels is different, or are they members of the hyposensitive group described by Libman?¹⁰ Martin and Gorham¹⁷ believe pain depends on coronary tension.

From a therapeutic standpoint, it seems to be extremely important to be cognizant of the possibility of coronary occlusion and myocardial infarction in the absence of pain. Vague symptoms of weakness, etc. in patients with hypertension or the onset of increased dyspnea, together with progressive failure in patients with previous mild failure, should make one alert to this serious condition. Putting the patient to bed and checking with serial electrocardiograms seem highly desirable.

The corollary may be equally true. Any patients with the typical pain of coronary insufficiency but no other suggestive clinical findings, even in the absence of changing T-waves in the electrocardiograms must be considered as possible cases of coronary occlusion without myocardial infarction and treated accordingly. This means total bed rest for a week or 10 days as a myocardial infarction might be developing. In these instances, clinical judgment is of much more importance than the electrocardiograms.

SUMMARY

Painless coronary occlusion and myocardial infarction are discussed. A review of 49 cases of proved myocardial infarction, 13 without pain, is presented.

BIBLIOGRAPHY

- 1 BLUMGART, H. L., SCHLESINGER, M. J., and DAVIS, D. Studies on the relation of the clinical manifestations of angina pectoris, coronary thrombosis and myocardial infarction to the pathologic findings, *Am Heart Jr*, 1940, xix, 1.
- 2 BLUMGART, H. L., SCHLESINGER, M. J., and ZOLL, P. M. Angina pectoris, coronary failure and acute myocardial infarction, *Jr Am Med Assoc*, 1941, cxvi, 91.
- 3 SMITH, F. M. Coronary artery disease, The diagnosis and treatment of cardiovascular disease, 1940, F. A. Davis Co., Philadelphia, p. 387.
- 4 LEVY, R. L. The diagnosis of coronary insufficiency, The diagnosis and treatment of cardiovascular disease, 1940, F. A. Davis Co., Philadelphia, p. 431.
- 5 WHITE, P. D. Heart disease, 1932, Macmillan Co., New York, p. 418.
- 6 EAST, C. F. T., BAIN, C. W. C., and CARY, F. L. Cardiac infarction without pain, *Lancet*, 1928, ii, 60.
- 7 BOYD, L. J., and WERBLOW, S. Coronary thrombosis without pain, *Am Jr Med Sci*, 1937, clxxxiv, 814.
- 8 WEDD, A. M. Painless coronary occlusion, *New York State Jr Med*, 1928, xxviii, 1091.
- 9 WIGSER, A. M. Silent coronary thrombosis with complete heart block and recovery, *Jr Med*, 1938, xviii, 364.
- 10 MORAWITZ, P., and HOCHREIN, M. Zur Diagnose und Behandlung der Koronarsklerose, *Munchen med Wchnschr*, 1928, lxxv, 17.
- 11 WILLIUS, F. A., and BROWN, O. E. Coronary sclerosis, an analysis of 86 necropsies, *Am Jr Med Sci*, 1924, clxviii, 165.

- 12 NATHANSON, M H Disease of coronary arteries, clinical and pathological features, Am Jr Med Sci, 1925, clxx, 240
- 13 POLLARD, H M, and HARVILL, T H Painless myocardial infarction, Am Jr Med Sci, 1940, clxxxxix, 628
- 14 KENNEDY, J A The incidence of myocardial infarction without pain in 200 autopsied cases, Am Heart Jr, 1937, xiv, 703
- 15 GORHAM, L W, and MARTIN, S J Coronary occlusion with and without pain, Arch Int Med, 1938, lxi, 821
- 16 LIBMAN, E Observations on individual sensitiveness to pain, Jr Am Med Assoc, 1934, cli, 335
- 17 MARTIN, S J, and GORHAM, L W Cardiac pain, Arch Int Med, 1938, lxi, 840

THE EFFECT OF THIAMIN ON THE RESIDUAL NEURAL DISTURBANCES OF TREATED PERNICIOUS ANEMIA¹

By J C ZILLHARDT, M.D., *Binghamton, N Y*, KEITH MACLEAN, M.D.,
Vancouver, B C, and WILLIAM P MURPHY, M.D.,
Boston, Massachusetts

By supplying sufficient amounts of anti-pernicious anemia substance it is possible to control the neural disturbances of uncomplicated Addisonian anemia. Certain residual neural manifestations are apt to remain, however, in spite of adequate liver therapy. This is particularly true in patients with advanced nervous system involvement and in those who have not been adequately treated at the onset.

Considerable thought has been given the various vitamins^{1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11} in connection with pernicious anemia and its associated neural disturbances. At the blood clinic of the Peter Bent Brigham Hospital interest became focused on vitamin B₁ and studies were carried out in an attempt to determine what relationship, if any, the administration of this vitamin might have on remaining neurological manifestations of pernicious anemia that had been adequately treated over a period of time.

The term "adequate treatment" implies "that each patient receives an amount of potent substance sufficient to produce and maintain a normal state of blood in order to insure the maintenance of the best possible state of health. This may be accomplished by giving each patient exactly that amount of anti-pernicious anemia substance which will be in excess of that which is necessary to maintain a level of 5,000,000 red blood cells per cubic millimeter in practically all patients. In a few patients it may be impossible to maintain the blood at or above the 5,000,000 level, and it may be concluded, therefore, that provided that the blood is otherwise normal in every respect (and no complicating factors exist) a lower level is normal for them."¹²

All patients used in this study of the effect of vitamin B₁ on residual neural involvement of adequately treated pernicious anemia are represented by number in the accompanying table (table 1). In every instance neurological manifestations were present at the time the diagnosis of pernicious anemia was first made and in none had there been an aggravation of the neural complications once adequate liver therapy was instituted. On the contrary with such treatment all showed a striking initial improvement of the neural disturbances. This improvement eventually eased off to a more or less stationary level and there resulted certain neurological symptoms and

* Received for publication March 30, 1940

From the Medical Clinic of the Peter Bent Brigham Hospital

TABLE I

Case Number	Age	Sex	Duration of Maintenance Treatment in Years	Average Erythrocyte and Hemoglobin Levels			
				Before Vitamin Therapy		During Vitamin Therapy	
				Millions	Grams	Millions	Grams
1	62	M	3	5 48	15 80	5 38	14 63
2	56	M	14	5 48	15 32	5 08	15 46
3	67	F	8	5 09	14 08	5 06	14 49
4	65	M	6	4 70	15 40	4 66	14 63
5	74	M	5	4 85	16 28	4 85	16 28
6	48	M	5	5 15	16 42	5 44	16 97
7	46	F	14	5 48	15 73	5 48	15 73
8	56	F	7	5 36	14 49	5 23	15 18
9	67	F	6	4 45	12 97	4 55	13 52
10	70	F	1	4 69	12 97	4 27	12 83
11	60	F	5	5 72	14 63	5 60	14 63
12	72	F	4	4 78	13 52	4 55	13 66
13	71	M	4	4 79	12 28	4 98	13 39
14	74	M	5	4 66	15 04	4 52	14 49
15	49	F	1	5 47	14 21	5 47	14 21
16	78	M	2	4 65	13 80	4 56	13 59
17	62	F	$\frac{1}{2}$	4 56	14 21	5 46	15 87
18	58	F	$\frac{1}{2}$	4 56	14 40	5 81	15 46
19	66	M	7	4 92	14 63	4 75	14 77

3 c c Conc Sol Liver Ext (Lederle) intramuscularly was used in the treatment of all above patients

signs that neither improved nor became aggravated as adequate liver therapy was maintained

What improvement in neural manifestations other than that, which they had already made, is possible in patients such as these in view of the probable pathological lesion in the nervous system? The neurological signs and symptoms of pernicious anemia are believed by various workers to be essentially due to

1 Such dysfunction of the end organs of the peripheral nerves as is supposed to occur in cases of severe anemia¹³

2 Degenerative changes in the peripheral nerves^{13, 14, 15, 16, 17, 18, 19} that may be due to the anoxia of marked anemia^{13, 15, 16} or in some cases to a food factor deficiency²⁰ or both

3 Edema of the cord associated with degenerative processes in the white matter¹⁷ In some acute cases this edema is believed to be marked and to be responsible for considerable neural disturbances¹³

4 Degenerative changes in the tracts of the spinal cord particularly those of the posterior and lateral columns

5 Structural changes within the brain

Keeping in mind the length of time that our subjects had been receiving adequate treatment it seemed quite probable that no manifestations were present as the result of anemia per se or as one might find in acute cases, also that whatever lesions existed in the central nervous system were quite permanent and irreversible

The chances then of doing more for these patients lay in

1 Prevention of any progression of the neural complications This was being taken care of by adequate liver treatment^{1,2}

2 Possibly in some way increasing the efficiency of the undamaged portions of the neural mechanism

3 Attempting cure of any reversible structural changes that might still be present in the peripheral nerves

4 Further improving the patients' well-being thereby possibly bettering neurological function

It might be well to mention here that in so far as could be determined, all of our patients had been on adequate diets since their first attendance at the blood clinic, and with scarcely an exception none was known to have had any serious dietary abnormality before The possibility, however, of a misleading history or improper absorption or poor utilization of some food factor was kept in mind

All the above aspects were carefully considered before the study was begun It seemed that any therapy, that would possibly be conducive to some further improvement in such cases as these, was worth while

The individuals under discussion had probably attained the maximal effect that liver therapy alone could produce particularly in so far as the neurological disturbances were concerned With this as a hypothesis it seemed reasonable to assume that, if a new therapeutic agent was added to the therapy already being instituted, whatever further improvement should occur must be related to the physical or psychological action of the new therapeutic agent

At the time the study was started, as has been mentioned, all subjects had been receiving adequate pernicious anemia therapy This therapy was continued just as it had been in the past In addition, patients 1 to 7 inclusive were given thiamin * 1 c c intramuscularly three times per week for four months The preparation used contained 10 milligrams or 3,000 international units of thiamin (crystalline vitamin B₁) per cubic centimeter Patients 8 to 14 inclusive were given 3 mg of thiamin * twice a day by mouth for four months Each milligram of this preparation contained 330 international units Patients 15 to 19 inclusive acted as controls They were given 1 c c of normal saline intramuscularly three times per week in addition to the liver treatment

Due regard was given to the possible psychological effects of this treatment and every effort was made to guard against them To all patients including the controls it was explained at the start that in addition to the liver treatment which they were receiving, they were to be given a new therapeutic agent that might or might not bring about further improvement The physician took care not to show any enthusiasm in regard to the new medicine or

*Furnished by Lederle Laboratories, Inc

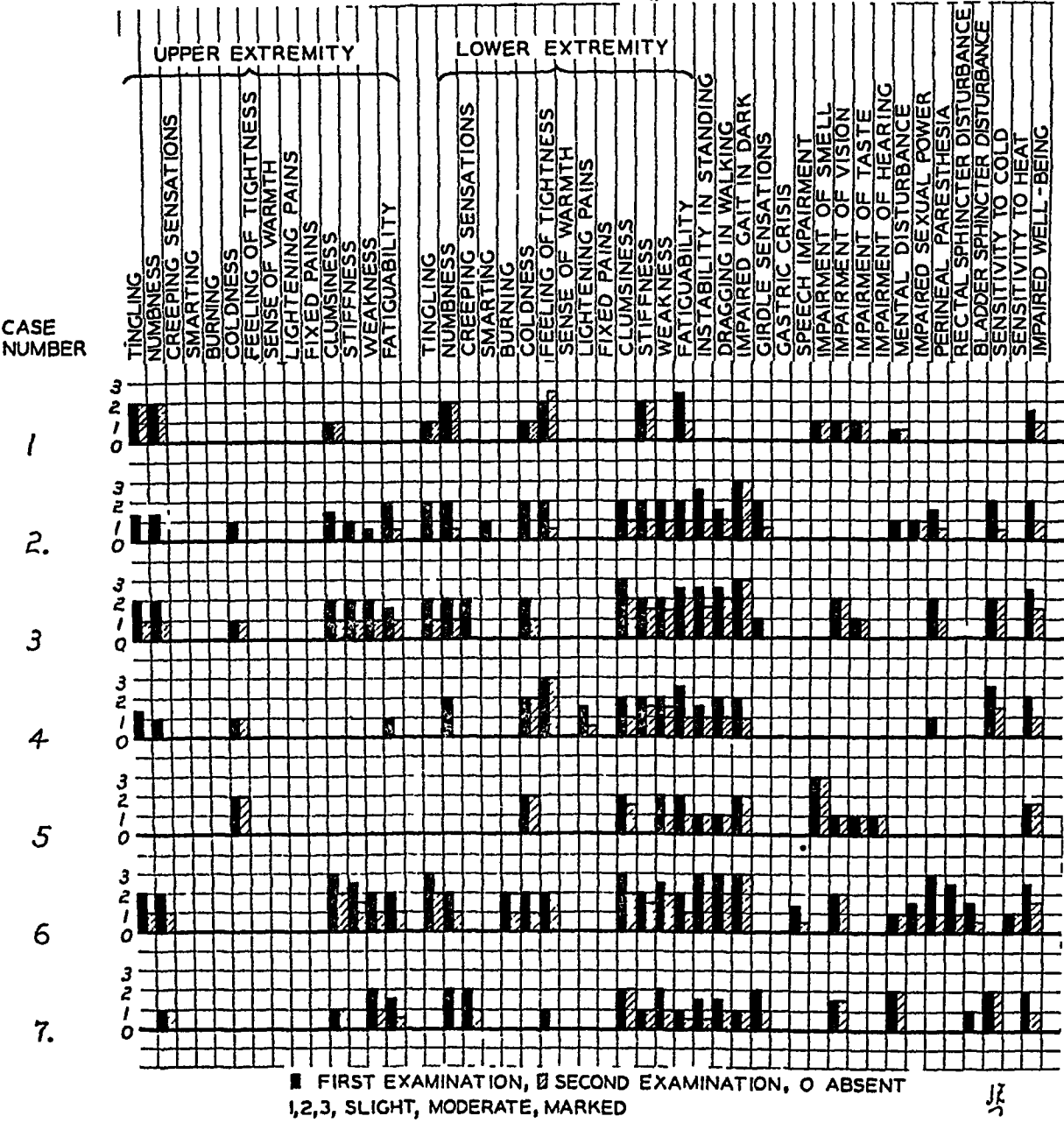


FIG 1

in any way unduly raise the patient's hopes Effort was made to give each patient approximately the same amount of attention at each office visit

All subjects had had physical examinations from time to time at the outdoor clinic Also many had had careful study as patients in the hospital The neurological portion of the more recent of these examinations checked favorably with our initial findings In our study the neurological examinations were performed by two physicians and were carried out partly or completely in duplicate as the individual case warranted The examinations necessarily were quite lengthy If it were felt that the subject was becoming unduly fatigued, he was allowed to go home and the examination was com-

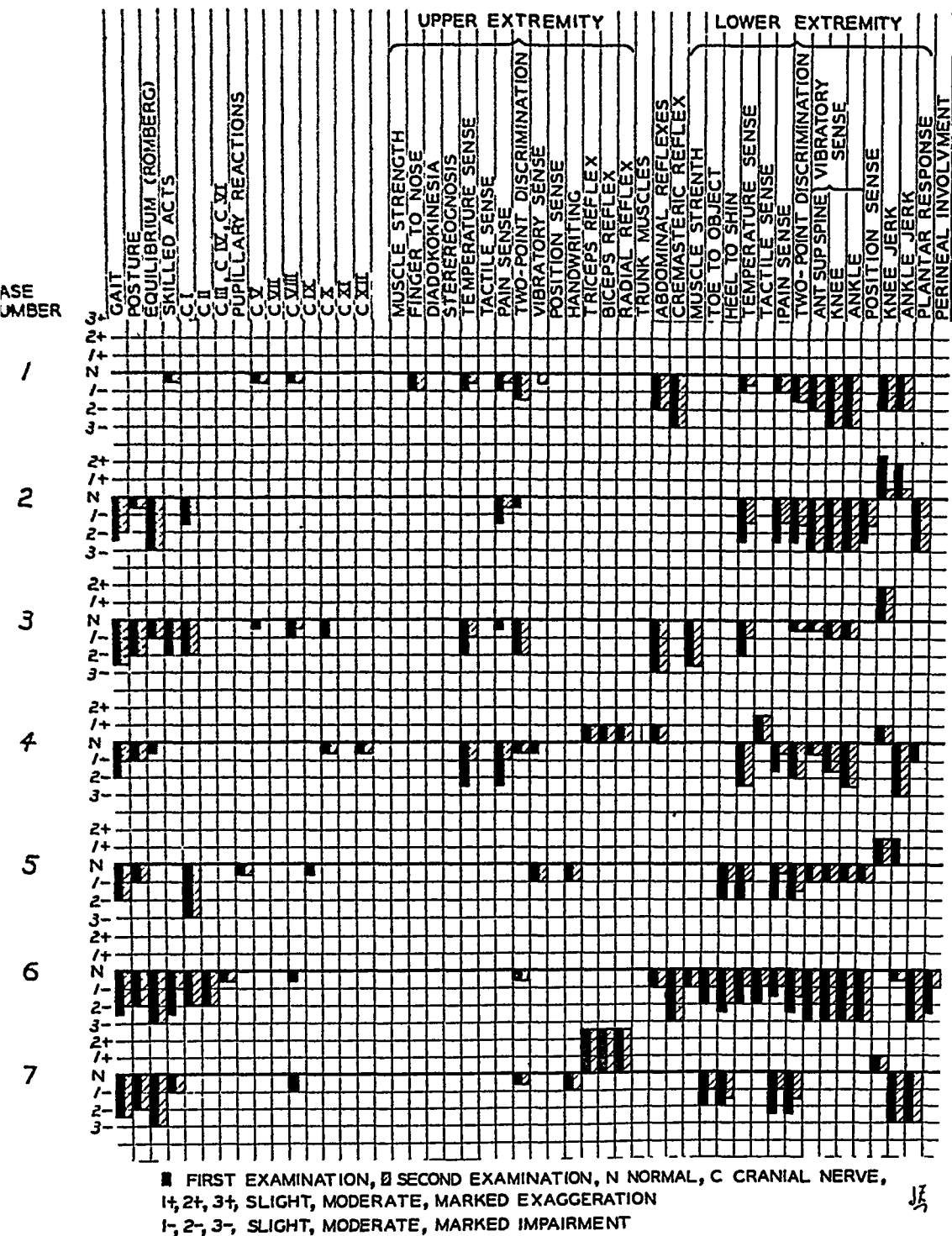


FIG 2

pleted at a subsequent visit. Each of the 19 individuals was examined when treatment was first begun. They were examined a second time at the end of two months and a third time two months later. That is each patient received three examinations during the four month period of treatment.

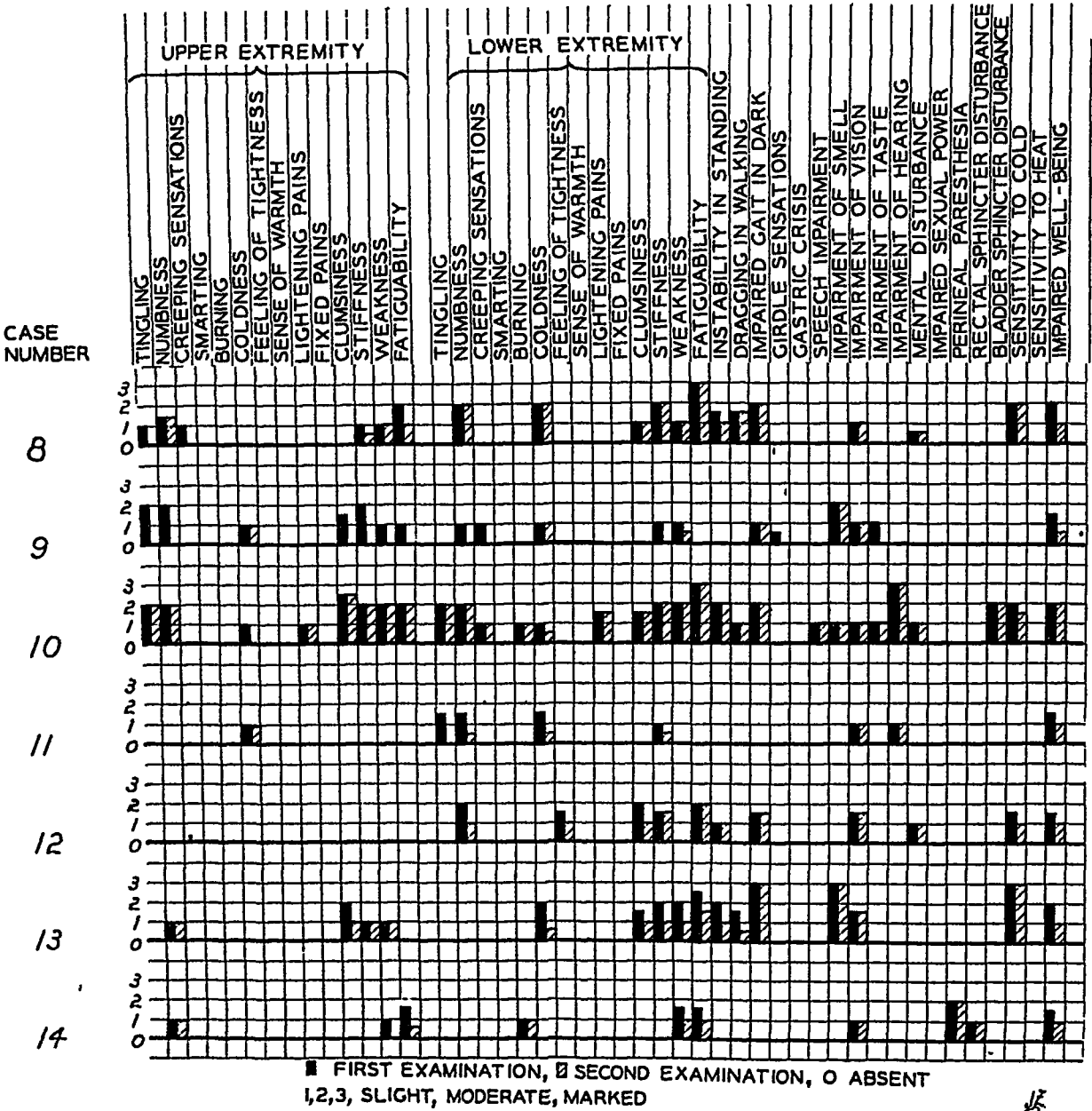


Fig 3

One very interesting observation was the fact that in all of the 19 cases there was little or no difference in the findings of the last examination as compared with the second. In other words it seemed that whatever changes occurred during the four month period of treatment were present at the end of the first two months. Little, if any, variation of symptoms or signs seemed to occur during the second two month period. Because of the similarity of the findings of the second and third examinations, the latter was omitted from the accompanying figures.

Figure 1 illustrates the subjective findings of those patients who received thiamin intramuscularly. With the exception of individuals 1 and 5 all experienced symptomatic improvement with treatment. Numbness and ting-

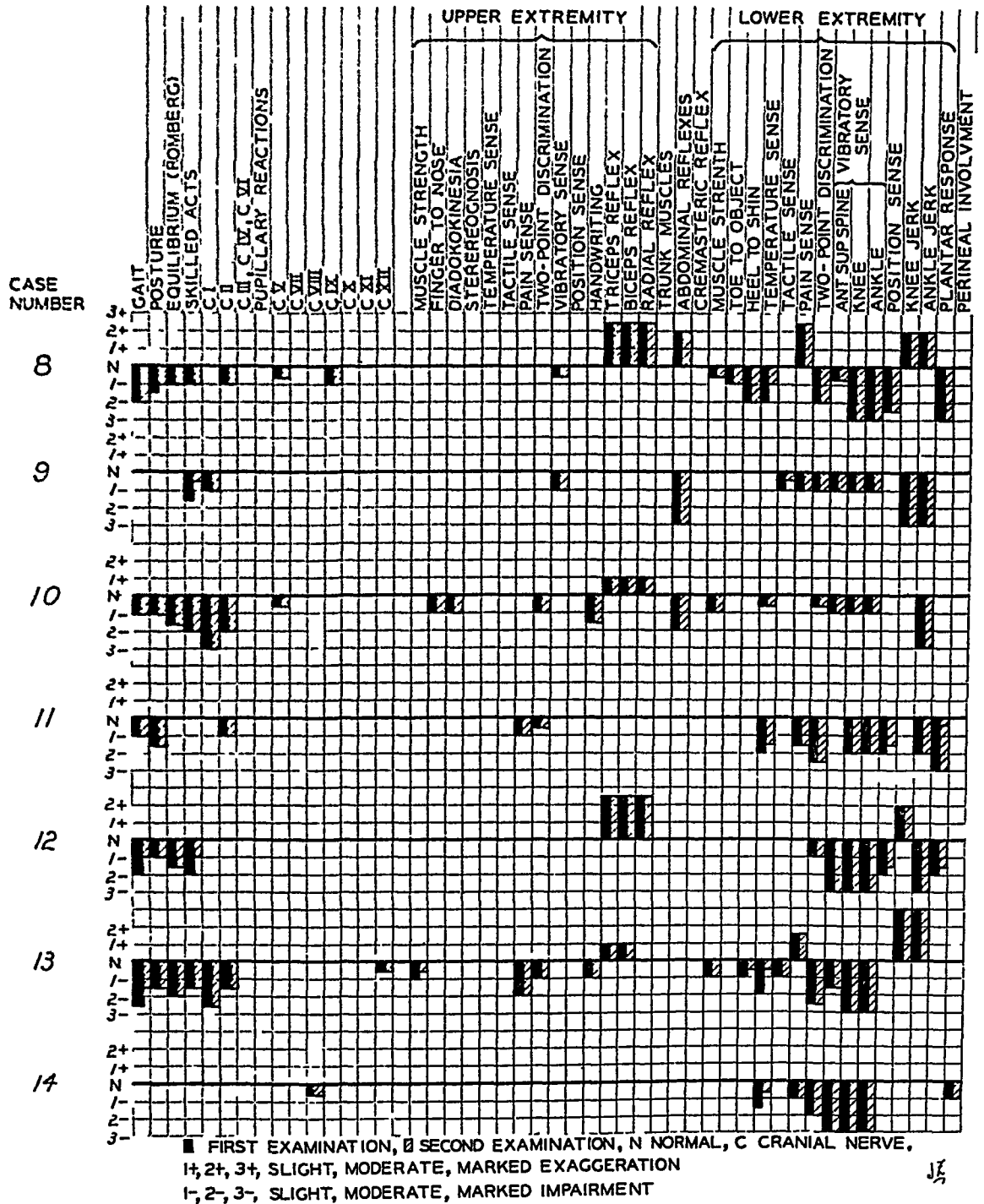
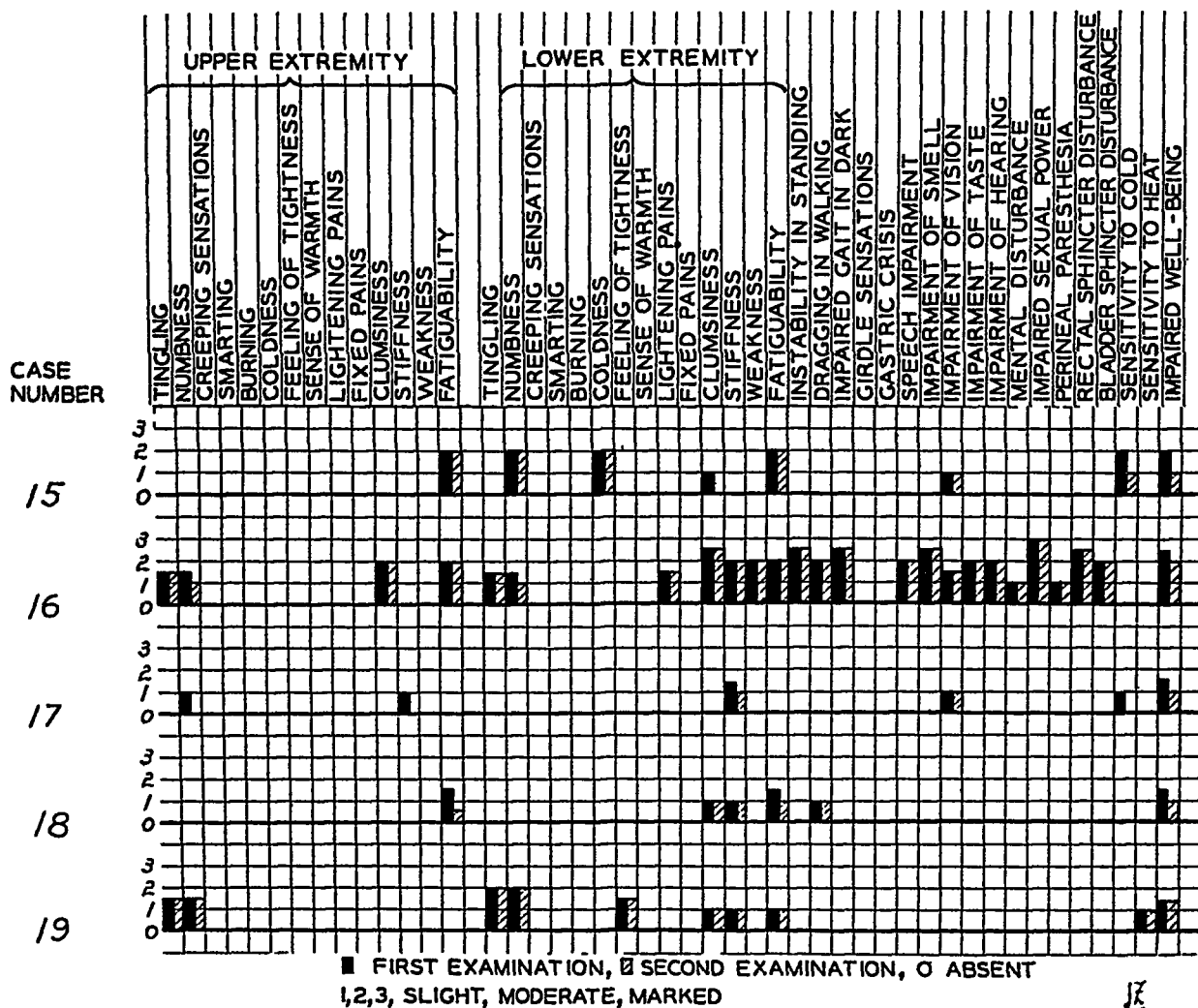


FIG 4

ling were diminished as was burning, when this was present. Those who were troubled with clumsiness, stiffness, weakness or fatigability of the extremities were convinced that these symptoms became less marked. There was likewise improvement in equilibrium. No change in the special senses occurred where these were involved. Improvement in perineal paresthesia



was noted in individuals 2, 3, 4 and 6. One patient, 6, who was insensible to movement of the bowels felt that this difficulty greatly subsided. Sensitivity to cold became less marked in two instances.

It will be seen from figure 2 that the principal improvements found on physical examination were in temperature sense, pain sense and in two point discrimination. The toe to object test and heel to shin test were carried out more accurately in a few instances. Patient 6 had considerable perineal anesthesia that became less marked after treatment. This man also seemed to show some improvement in vibratory sense over the anterior superior iliac spines, as determined with a calibrated tuning fork. In patient 4 an abnormal plantar response was present on first examination. Some improvement in position sense of the toes was found in individual 2. This man had considerable exaggeration of the knee and ankle jerks on first examination. Patellar clonus was elicited at that time. These reflexes gradually improved to the point where they were considered but slightly hyperactive.

Figures 3 and 4 show the results of the examinations of those who were

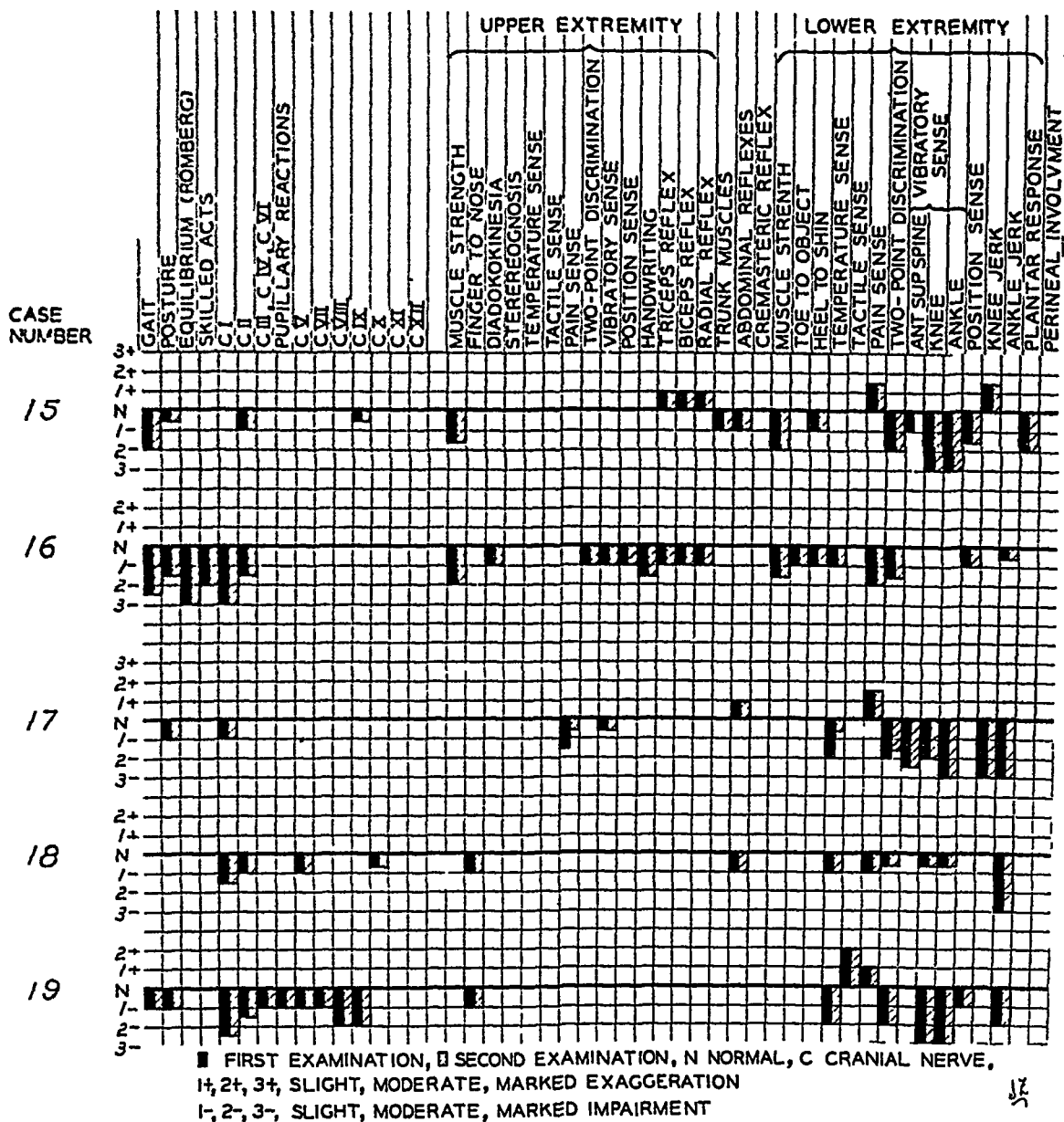


Fig 6

given thiamin by mouth. With the exception of improvement in well-being it will be noted that little change occurred during the period of therapy.

Figure 5 indicates the symptoms and figure 6 the signs of those pernicious anemia patients who acted as controls. This is the group that was given normal saline intramuscularly three times per week. At the time of the second examination all of these individuals stated that they felt better in general, yet on further questioning there was little or no change in any of the individual subjective items as shown in the figure. It can also be seen that with the exception of patient 17 no objective changes occurred as result

of treatment It is interesting to note that patient 17 showed improvement in pain sense, temperature sense and two point discrimination

One has to be cautious in drawing conclusions from a study of this kind Attempting to quantitate neurological symptoms and signs is a task that is subject to error under the most ideal circumstances The intelligence and cooperation of the patient, as well as the judgment and patience of the physician are important factors The element of disposition and of physical and mental fatigue on the part of both patient and examiner as well as the inaccuracy of existing procedures of examination come into play The many possible variables are only too familiar to those who have occasion to do neurological studies It is therefore with some reserve that an attempt is made to interpret our findings

The administration of thiamin intramuscularly seemed to have some therapeutic effect in most of the patients who received it Possibly in a larger series of cases, however, the results would not be so favorable Yet it is conceivable that with such treatment the efficiency of undamaged neural tissue might become increased or existing reversible peripheral neuritic changes might become improved, or as a result of possible improvement of the patient's general health, neural function might become enhanced

It is difficult to explain why the giving of thiamin by mouth was not as effective as when it was given intramuscularly Those patients who took the medication orally were considered dependable They were selected with this particular point in mind, yet it is possible that they did not give their full cooperation The possibility of improper absorption or poor utilization of thiamin as given by mouth must be considered

SUMMARY

1 Our results suggest that the administration of thiamin might have a beneficial effect on those residual neural signs and symptoms of pernicious anemia that seemed stationary in spite of persistent, intensive anti-pernicious anemia therapy

2 Our study would indicate that 3,000 international units of thiamin intramuscularly three times per week is more effective than 990 international units of thiamin by mouth twice a day

3 In those instances in which neurological improvement took place the maximal beneficial effect occurred during the first two months of treatment Continued use of thiamin after this period seemed to produce no further change

4 The many variables that are involved in attempting to quantitate neurological symptoms and signs were carefully considered in this study

We are very grateful to Miss Isabel Howard for her most valuable laboratory assistance

BIBLIOGRAPHY

- 1 CONNOR, H M Improvement of neurologic manifestations of pernicious anemia, *Proc Staff Meet Mayo Clin*, 1928, iii, 454
- 2 GARFAN, P H, LEVIN, P M, and GUITER, E I The effect of liver therapy on the neurologic aspects of pernicious anemia, *Ann Int Med*, 1933, vi, 1441
- 3 GIBBS, E F, KATTWINKEL, E E, and CASTLE, W B Experimental combined system disease, *New Eng Jr Med*, 1930, ccii, 523-527
- 4 GIBBS, E F, CASTLE, W B, GIBBS, E F, and COBB, S Neuropathology of experimental vitamin deficiency, *Am Jr Path*, 1935, vi, 669
- 5 BEGG, A Ein Behandlungserfolg bei funikulärer Myelose mittels Vitamin B₁ (Betabion), *Deutsch med Wchnschr*, 1936, lxi, 1643
- 6 LASCH, F Ein erfolgreich mit Vitamin B₁ behandelter Fall von schwerer funikulärer Myelose, *München med Wchnschr*, 1936, lxxviii, 1390
- 7 WILLIAMS, R R, and SPIES, T D Vitamin B₁ and its uses in medicine, 1938, Macmillan Company, New York
- 8 WINTROBE, M M, MITCHELL, D M, and KOLB, L C Sensory neuron degeneration in deficiency, *Jr Exper Med*, 1938, lxxiii, 207-220
- 9 MILLER, D K, and RHODES, C P The experimental production of loss of hematopoietic elements of the gastric secretion and of the liver in swine with achlorhydria and anemia, *Jr Clin Invest*, 1935, xiv, 153
- 10 MIFLANBY, E The experimental production and prevention of degeneration in the spinal cord, *Brain*, 1931, liv, 247
- 11 SUZMAN, M M, MULLER, G L, and UNGLEY, C C An attempt to produce spinal cord degeneration in dogs fed a high cereal diet deficient in vitamin A, *Am Jr Physiol*, 1932, ci, 529
- 12 MURPHY, W P Anemia in practice, 1939, W B Saunders Co, Philadelphia
- 13 GRINKER, R R. Neurology, 1937, Charles C Thomas, Springfield, Ill
- 14 GREENFIELD, J G, and O'FALLON, E Subacute combined degeneration and pernicious anemia, *Lancet*, 1933, ii, 62
- 15 COHEN, H Subacute combined degeneration of the spinal cord, *Lancet*, 1935, i, 1291
- 16 GRINKER, R R, and KANDFL, E Results of treatment of the neurologic complications of pernicious anemia, *Arch Int Med*, 1934, liv, 851
- 17 BRAIN, W R Subacute combined degeneration, Oxford University Press, New York
- 18 KENNEDY, FOSTER Cecil, Text Book of Medicine, 1937, W B Saunders Co, Philadelphia
- 19 BRAIN, W R Subacute combined degeneration, *Brit Med Jr*, 1935, ii, 1056
- 20 GREENFIELD, J G, and CARMICHAEL, E A The peripheral nerves in cases of subacute combined degeneration of the cord, *Brain*, 1935, lviii, 483

THE EFFECT OF A VITAMIN B COMPLEX ON THE RESIDUAL NEURAL DISTURBANCES OF TREATED PERNICIOUS ANEMIA *

By J C ZILLHARDT, *Binghamton, N Y*, ISABEL HOWARD, and WILLIAM P MURPHY, *Boston, Massachusetts*

UPON completion of the study of the effect of thiamin on the residual neural disturbances of treated pernicious anemia the experiment was repeated under the same conditions using a vitamin B complex. A group of 13 patients was used in this work. As with the individuals treated in the aforementioned study, neurological manifestations were present at the time the diagnosis of pernicious anemia was first made. With adequate liver therapy there was improvement of the neural disturbances. This improvement had tapered off to a more or less stationary level and there remained neural signs and symptoms that neither improved nor became aggravated as adequate liver treatment was maintained.

Seven of this group were given 1 c c of a vitamin B complex † intramuscularly three times per week for three months in addition to continued adequate liver therapy. Each cubic centimeter of this preparation contained thiamin (crystalline B₁) 2 mg or 600 international units, riboflavin (B₂) 0.3 mg or 100 Bourquin-Sherman rat growth units, nicotinic acid 10 mg, dermatitis factor (B₆) 30 "rat day" units, filtrate factors approximately 30 "chicken growth" units. The other six patients acted as controls. They were given 1 c c of normal saline intramuscularly three times per week. Again adequate pernicious anemia therapy was maintained in each instance.

Neurological examinations were carried out in the same manner and at the same intervals as described in the previous study. At the end of the course of treatment an analysis of the examinations showed that with the exception of some improvement in well being the group that received the vitamin B complex showed little change in subjective and objective signs in comparison with the control group.

* Received for publication March 30, 1940

From the Medical Clinic of the Peter Bent Brigham Hospital

† Furnished by Lederle Laboratories, Inc

THE SYNDROME OF MULTIPLE VITAMIN DEFICIENCY ¹

By V P SYDLASTRICKER, M D , F A C P , *Augusta, Georgia*

Good nutrition depends not only on the intake of sufficient amounts of all the substances required for normal metabolic processes but also on their adequate absorption, storage and utilization. In the case of most of the vitamins it is probable that optimal intake varies with the demands of the body for energy production, repair or growth. The requirements for some members of the B group are definitely dependent on the composition of the diet and it is likely that there are interrelations or synergistic reactions between vitamins which further condition the requirements ^{1, 2, 3, 4}

The development of avitaminosis is due to the failure or perversion of normal biochemical reactions which can be completed only when adequate supplies of vitamins are available. The functions of the water soluble and fat soluble vitamins seem to be very different. The B group of vitamins is necessary for the derivation of energy from carbohydrate and riboflavin may also be concerned in the utilization of fat ⁵ and in cellular respiration in the absence of haem. Ascorbic acid is thought to be important in various oxidation-reduction processes of cells and, in addition, is necessary for the formation of the intercellular cement-substance in all tissues. The fat soluble vitamins A, D, E and K seem to be requisite for the maintenance and repair of certain specialized tissues and the production of various physiologically indispensable substances. The water soluble vitamins as a group are rapidly absorbed to the point of saturation or of the limitations of storage, after which additional amounts ingested are excreted in the urine. It is likely that storage is never great because depletion can be brought about relatively quickly. The fat soluble group seems to be absorbed slowly but stored in considerable amounts so that depletion is seldom acute. An exception is vitamin K which is absorbed and utilized quite rapidly in the presence of adequate amounts of bile and which can be depleted very quickly when bile is absent from the duodenum.

Ever since the recognition of the classic deficiency diseases it has been customary to regard them as specific clinical and etiologic entities though variations in the pattern of each one have been noted by innumerable observers. When pure synthetic vitamins became available it was found that appropriate therapy with a single vitamin usually produced rapid and complete cure of the major manifestations of each of the avitaminoses but that certain other symptoms or signs might persist or grow worse ^{6, 7, 8}. Often

* Read at the Boston meeting of the American College of Physicians, April 23, 1941

From the University of Georgia School of Medicine and the University Hospital, Augusta, Ga

such residual phenomena were referable to known vitamin deficiencies and responded to specific treatment, but their presence confirmed the suggestion by earlier observers that more than one factor might be concerned in the production of a typical deficiency syndrome^{9, 10, 11} Recent observations on the effect of deprivation of a single vitamin in normal human subjects maintained on carefully controlled diets have shown that it is quite difficult to produce the syndromes of pellagra,^{12, 13} beri-beri^{14, 15, 16} and scurvy^{17, 18} by this means Such results are not surprising since consideration of the background of spontaneous avitaminosis shows that depletion occurs either from very prolonged partial deficiency of intake or absorption of many vitamins or from great increase in requirements often in the presence of sudden and sometimes complete failure of intake or absorption

It is traditional and correct to relate the incidence of vitamin deficiency to inadequate or unbalanced diet Wherever endemic avitaminosis occurs, whether the prevailing pattern be that of pellagra, ariboflavinosis, beri-beri, scurvy or xerophthalmia, it is found that the food habits of the population result in the widespread use of excessive amounts of refined carbohydrates, suboptimal quantities of fat and quite deficient protein Along with this goes minimal consumption of protective foods Local custom may be very important in determining the clinical manifestations of endemic deficiency The choice of hominy grits or of rice seems to determine the prevalence of pellagra or of beri-beri Where collards replace cabbage as the staple green-stuff of the poor, evidences of vitamin A deficiency are distinctly rare¹⁹ Similarly deficient diets are often the result of individual choice or of physicians' instructions among persons not influenced by local custom and not subject to economic stress, dietary vagaries and poorly planned regimens for the treatment of peptic ulcer, heart disease or nephritis are frequent examples It is obvious that the effect of a high-carbohydrate vitamin-poor diet is two-fold it not only fails to supply adequate amounts of all vitamins but actually increases the requirement for the B group

The use of an unbalanced diet seldom or never results in acute or solitary avitaminosis since no naturally selected combination of foods is apt to be completely lacking in a single vitamin It seems likely that prolonged partial deficiency produces functional and organic changes in the digestive tract which interfere with the absorption and utilization of the small amounts of vitamins available so that eventually a critical level is reached The acute and often apparently uncomplicated manifestations of avitaminosis are apt to result from sudden large requirements for vitamins produced by the substitution of alcohol for food, maintenance on dextrose or severe febrile disease.

The relation of gastrointestinal disturbances and diseases of the liver and bile ducts to vitamin deficiencies has been stressed by many observers^{20, 21, 22} Anorexia resulting from organic disease of any part of the digestive tract diminishes food intake and is particularly apt to result in poor consumption of meats and vegetables Present knowledge would in-

dicate that gastric achlorhydria interferes with the extraction of the entire water-soluble group of vitamins from food and that biliary obstruction with lack of bile in the upper bowel prevents adequate absorption of the fat soluble group. Gastric achlorhydria is common in all the avitaminoses and may be a result of chronically deficient diet as well as a factor contributing to disease.²⁷ Vomiting and diarrhea have long been recognized as causes of partial loss of ingested vitamins and edema of the gastrointestinal tract from any cause can prevent absorption. Diseases of the liver including fatty infiltration and chronic passive congestion prevent the cleavage of carotene into vitamin A, the synthesis of prothrombin in the presence of vitamin K and the adequate storage of all the known vitamins. Hepatic disease also may interfere with the utilization of thiamin, nicotinic acid and other members of the B group by retarding or preventing the formation of their physiologically active compounds. It seems quite certain that such intrinsic disorders are as unlikely to produce an uncomplicated avitaminosis as is faulty diet.

Interpretation of the clinical manifestations of a specific vitamin deficiency is based on evidence which frequently is incomplete. Accurate information can be obtained only by maintaining normal human subjects on diets so constructed and supplemented as to be deficient only in the substance under investigation. This is a formidable and frequently impossible task and such experiments are necessarily relatively brief. The effect of partial deficiency persisting for years rather than weeks or months cannot be expected, nevertheless much important information has been gained by this method. Hecht and Mandelbaum²¹ were able to demonstrate that the earliest sign of vitamin A deficiency is delay in dark adaptation. Sebrell and Butler^{12, 13} separated the syndrome of ariboflavinosis from pellagra and also showed that typical pellagrous dermatitis resulted from nicotinic acid deficiency. Williams and his collaborators^{15, 16} and Jolliffe and others¹⁴ have identified certain symptoms and signs of thiamin deficiency and Lund and Crandon and Dill^{17, 18} were able to prove that some of the manifestations of scurvy can be produced by relatively short periods of ascorbic acid deprivation. Most of the criteria by which we identify specific deficiencies are derived from much less certain methods. The usual procedure is to maintain patients with frank deficiency disease on a grossly inadequate diet of known composition and to add vitamins seriatim, observing the effects of treatment. Even less satisfactory is the administration of a single vitamin to persons with multiple deficiencies. It is often impossible to evaluate results with either regimen because increased food intake from improved appetite may follow administration of any of the water soluble vitamins and particularly because we know little or nothing of the synergistic action of vitamins.

Brief consideration of the symptomatology of deficiency disease reveals the complexity of clinical pictures which result from deficiency of several vitamins usually at different levels of depletion. Weakness, nervous irritability, vague malaise, lassitude, muscle pains, anorexia and disturbances of gastrointestinal motility have been described as early manifestations of

vitamin A deficiency, beri-beri, pellagra, rickets and scurvy. They have been shown to occur in uncomplicated experimental thiamin deficiency^{14, 15, 16} and probably reflect the metabolic defect of this avitaminosis at an early or physiologic stage. Photophobia, irritation of the eyes, blurring of vision, rapid visual fatigue, poor vision in dim light and night blindness are well recognized symptoms of vitamin A deficiency. Night blindness is specific, and delayed dark adaptation has been proved the earliest sign of avitaminosis A²⁴ but the other symptoms are frequent in pellagra and beri-beri where they are due to a complicating riboflavin deficiency. Mental confusion, forgetfulness, confabulation, depression, psychosis and stupor are common in pellagra and not infrequent in beri-beri. Often they occur in the absence of any physical sign of either disease. Frequently the rapid cure of such mental symptoms with nicotinic acid indicates that they are evidence of disturbed nutrition of cerebral neurones resulting from nicotinic acid deficiency^{25, 26, 27}. Nervous and neuro-muscular symptoms very similar to those attributed to mild grades of thiamin and nicotinic acid deficiency but responding to neither have been relieved promptly by vitamin B₆^{28, 29}.

In appraising the presenting physical signs of vitamin deficiency in any given case it is necessary to follow rather arbitrary criteria derived from clinical as well as experimental observation. Signs generally associated with thiamin deficiency are tenderness of nerves and of the calf muscles, hyperreflexia and hyporeflexia, muscular weakness and edema. Later, sensory disturbances and actual loss of motor function with or without cardiac manifestations are found. Not infrequently edema and tachycardia followed by other signs of heart failure dominate the picture. This is not the place to discuss the question of the specificity of all these signs^{10, 30} since no better etiology has been offered. The diagnosis of nicotinic acid deficiency requires the presence of characteristic symmetrical dermatitis, of glossitis with atrophy of the lingual papillae, of lesions of the buccal mucosa or genitalia. With these there is almost invariably some part of the picture of mental disturbance already noted. The syndrome of ariboflavinosis presents cheilosis, glossitis, various grades of superficial vascularizing keratitis and seborrheic lesions of various sorts. The diagnosis of scurvy is made on the occurrence of gingivitis, hemorrhages into the mucous membranes, skin and tissues in general and, theoretically, a plasma ascorbic acid level of zero. Vitamin A deficiency is recognized by follicular keratosis or xerosis of the skin and cornea, delayed dark adaptation and low values for vitamin A and carotinoids in the blood. Evidence of lack of vitamin D in the adult is based on radiographic signs of loss of calcium from the bones and on abnormal phosphatase values in the blood.

It is notable that in clinical experience few patients present all the signs attributed to any single avitaminosis but that almost every one when examined with care shows those of several.

Certain patterns are much more common than others and these are mainly multiple B group deficiencies. Classical pellagra quite regularly presents the

cheilosis and corneal vascularization of ariboflavinosi and the muscle tenderness and reflex disturbances of thiamin deficiency. Less often there is edema due neither to protein deficiency, nor actual peripheral neuritis. Patients with frank beriberi of either the wet or dry type seldom fail to show either the skin lesions or the glossitis of nicotinic acid deficiency and often there is cheilosis and the eye signs of ariboflavinosi. These combinations are of course to be expected from the nature of the etiology of B group deficiency. Rarely individuals with one of these syndromes has signs of vitamin A deficiency as well. This association is unusual in our locality. An occasional example is seen of an apparently acute phase of multiple avitaminosis which has been described as common in the tropics^{31, 32} but which is rare in this country. This syndrome consists of severe ocular lesions and cheilosis similar to those of ariboflavinosi, ulcerative and atrophic glossitis, ulcerative dermatitis of the genitalia and vesicular dermatitis of the trunk and extremities such as are seen in severe nicotinic acid deficiency, follicular keratosis and a neuropathy of the optic nerve with swelling and congestion and marked dimness of vision. Such individuals have been too ill for experimentation but the very prompt cure of all lesions except follicular keratosis with large amounts of synthetic thiamin, nicotinic acid and riboflavin would seem to indicate that lack of these vitamins is the main fault. It is impossible to identify the factor responsible for the optic neuropathy with marked impairment of visual acuity and contraction of color fields. In our experience scurvy in adult patients is frequently associated with glossitis, ocular signs, dermatitis or reflex changes characteristic of deficiency of one or another member of the B group. What seems of more significance is that we have not seen a patient with clinical scurvy who had plasma ascorbic acid below 0.15 milligram per cent. It is likely that the associated B group and perhaps vitamin A deficiency play an important part in the development of scorbutic lesions.³³

Though absolute proof cannot be presented, both clinical observation and therapeutic tests indicate that the presence of signs of any of the avitaminoses is indicative of multiple deficiency. In the case of the B group, treatment with the single vitamin indicated by predominant signs may result in the rapid development of severe manifestations of other deficiencies. In the majority of instances signs of multiple deficiency can be found without difficulty.

It is trite but necessary to say that a high protein, high caloric diet containing adequate amounts of the protective foods is the basis of all treatment of deficiency disease. The components of such a diet can be varied to suit the needs of the given case. Frequently it must be liquid and given in small amounts at frequent intervals through an indwelling nasal tube for several days. Such a diet should be supplemented with yeast or crude liver extracts and relatively huge amounts of the particular vitamin which seems to be predominantly lacking. In addition all other available vitamins should be given in amounts representing at least four or five times the normal daily requirement. In the case of the water-soluble group such massive dosage

is seldom required for more than a week though response may sometimes be quite slow in patients with beriberi or very chronic ariboflavinosis. Delayed response can be attributed to some intrinsic disturbance which interferes with absorption or utilization. When no definite effect is observed after three days of intensive therapy by mouth it is advisable to change to a parenteral route. Thiamin and riboflavin frequently produce almost immediate effects when given intramuscularly or intravenously after failure on peroral administration. It may be wise always to give these vitamins by injection to patients who are urgently ill. The saving of time and material more than outweighs the increased cost of injectable preparations.

BIBLIOGRAPHY

- 1 COWGILL, G R. The vitamin B requirements of man, 1934, Yale University Press, New Haven
- 2 SPIES, T D, VILTER, R W, and ASHE, W F. Pellagra, beriberi and riboflavin deficiency in human beings, *Jr Am Med Assoc*, 1939, cxiii, 931
- 3 SYDENSTRICKER, V P. Changing concepts of deficiency diseases, *Jr Med Assoc Alabama*, 1939, ix, 365
- 4 SPIES, T D, HIGHTOWER, D P, and HUBBARD, L H. Some recent advances in vitamin therapy, *Jr Am Med Assoc*, 1940, cxv, 292
- 5 MANNERING, G J, LIPTON, M A, and ELVEHJEM, C C. Relation of dietary fat to riboflavin requirement of growing rats, *Proc Soc. Exper Biol and Med*, 1941, xlv, 100
- 6 SCHMIDT, H L, and SYDENSTRICKER, V P. Nicotinic acid in the prevention of pellagra, *Jr Am Med Assoc*, 1938, cx, 2065
- 7 SPIES, T D, BEAN, W B, and ASHE, W F. Recent advances in the treatment of pellagra and associated deficiencies, *ANN INT MED*, 1939, xii, 1830
- 8 WEISS, S. Occidental beriberi with cardiovascular manifestations, *Jr Am Med Assoc*, 1940, cxv, 832
- 9 GOLDBERGER, J, WHEELER, G A, and SYDENSTRICKER, E. A study of the diet of non-pellagrous and of pellagrous households in textile mill communities in South Carolina in 1916, *Jr Am Med Assoc*, 1918, lxxxi, 944
- 10 WHELLER, G A. The pellagra preventive value of autoclaved dried yeast, canned flaked haddock and canned green peas, *Pub Health Rep*, 1933, xlviii, 67
- 11 SERRILL, W H. Vitamins in relation to the prevention and treatment of pellagra, *Jr Am Med Assoc*, 1938, cx, 1665
- 12 SERRILL, W H, and BUTLER, R E. Riboflavin deficiency in man, *Pub Health Rep*, 1938, liii, 2282
- 13 SERRILL, W H, and BUTLER, R E. Riboflavin deficiency in man, *Pub Health Rep*, 1939, liv, 2121
- 14 JOLLIFF, N, GOODHART, R, GENNIS, J, and CLINE, J K. The experimental production of vitamin B₂ deficiency in normal subjects, *Am Jr Med Sci*, 1939, cxviii, 198
- 15 WILLIAMS, R D, MASON, H L, and SMITH, B F. Induced vitamin B₂ deficiency in human subjects, *Proc Staff Meet Mayo Clin*, 1939, xiv, 787
- 16 WILLIAMS, R D, MASON, H L, WILDER, R M, and SMITH, B F. Observations on induced thiamin deficiency in man, *Arch Int Med*, 1940, lxx, 785
- 17 CHANDON, J H, LUND, C C, and DILL, D B. Human experimental scurvy, *New Eng Jr Med*, 1940, ccxxxiii, 353
- 18 LUND, C C, and CHANDON, J H. Human experimental scurvy, *Jr Am Med Assoc*, 1941, cxv, 663
- 19 Author's unpublished observations

- 20 EUSTEFMAN, G B, and O'LEARY, P A Pellagra secondary to benign and carcinomatous lesions and dysfunction of the gastrointestinal tract, Arch Int Med, 1931, xlvii, 633
- 21 STRAUSS, M B The role of the gastro-intestinal tract in conditioning deficiency disease, Jr Am Med Assoc, 1934, ciii, 1
- 22 MACKIE, T T, EDDY, W H, and MILLS, M A Vitamin deficiencies in gastrointestinal disease, ANN INT MED, 1940, xii, 28
- 23 SYDENSTRICKER, V P, et al : Treatment of pellagra with nicotinic acid, South Med Jr, 1938, xxxi, 1155
- 24 HECHT, S, and MANDERBAUM, J Rod-cone adaptation and vitamin A, Science, 1938, lxxviii, 219
- 25 SPIES, T D, ARING, C D, GRIFPERIN, J, and BLAN, W B The mental symptoms of pellagra, Am Jr Med Sci, 1938, cxvii, 461
- 26 CLECKLEY, H M, SYDENSTRICKER, V P and GIESLIN, L E Nicotinic acid in the treatment of atypical psychosis associated with malnutrition, Jr Am Med Assoc, 1939, cxvii, 2107
- 27 JOLLIFFE, N, BOWMAN, K M, ROSENBLUM, L A and FFIN, H D .Nicotinic acid deficiency encephalopathy, Jr Am Med Assoc, 1939, cxiv, 307
- 28 SPIES, T D, BEAN, W B, and ASHF, W F A note on the use of vitamin B₆ in human nutrition, Jr Am Med Assoc, 1939, cxvii, 2414
- 29 SPIES, T D, LADISH, R K, and BRAN, W B Vitamin B₆ (pyridoxine) deficiency in human beings, Jr Am Med Assoc, 1940, cxv, 839
- 30 MEKLEJOHN, A P Is thiamin the antineuritic vitamin? New Eng Jr Med, 1940, ccxliii, 265
- 31 SCOTT, H H An investigation into an acute outbreak of central neuritis, Ann Trop Med and Parasit, 1918, xii, 109
- 32 MOORE, D F Partial loss of central acuity of vision for reading and distance in school children and its possible association with food deficiency, West African Med Jr, 1930, iii, 46

GLUCOSE-SULFAPYRIDINE; EXPERIMENTAL AND CLINICAL STUDIES*

By HERBERT K ENSWORTH, M D , JAMES LIEBMANN, M D , MERTON C LOCKHART, PH D , and NORMAN PLUMMER, M D ,
New York, N Y

When satisfactory oral therapy with sulfapyridine is impossible, or when it is desired rapidly to obtain high blood concentrations of the drug, parenteral administration is necessary Sodium sulfapyridine may be used for this purpose, but may sclerose veins, or cause local necrosis from accidental extravasation In the search for soluble forms of the drug, preparations of sulfapyridine in glucose solutions have been made Blake and Haviland¹ were able to get 2 grams of sulfapyridine into solution in a liter of fluid containing equal parts of 5 per cent glucose in distilled water and physiological saline which had been brought to a boil By using more concentrated solutions of glucose, workers in the Research Division of the Lederle Laboratories were able to dissolve greater amounts of sulfapyridine, although boiling was necessary It was later discovered that a similar aqueous solution of sulfapyridine could be prepared with other aldohexoses or aldopentoses Concentrations of from 5 to 30 per cent of sulfapyridine could be obtained in from 30 to 50 per cent aldehydic-sugar water solution In this report the properties of glucose sulfapyridine will be described and clinical studies with a solution of 10 per cent sulfapyridine in 50 per cent glucose will be reported

The clear aqueous solution of 10 per cent sulfapyridine in 50 per cent glucose varies from a light-yellow to brown in color, contains some uncombined sulfapyridine, usually in the order of from 5 to 10 per cent of the total sulfapyridine content and some uncombined glucose, but about 90 per cent of the total sulfapyridine is in the form of a complex, believed to be a Schiff's base† On hydrolysis of this complex, by dilution, acidification or heating of the diluted complex, free sulfapyridine is obtained

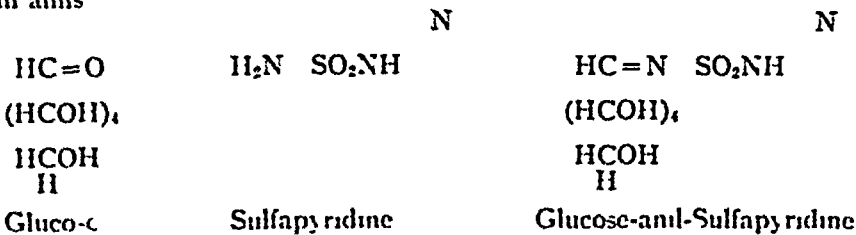
* Received for publication December 10, 1940

From the First (Columbia) and Second (Cornell) Medical Divisions, Bellevue Hospital, the Departments of Medicine of the College of Physicians and Surgeons, Columbia University and Cornell University Medical College

The chemical and animal studies were done at the Lederle Laboratories (Dr Lockhart)

The clinical studies were conducted under a grant of the Josiah Macy, Jr Foundation

† A Schiff's base may be designated as the reaction product of an aldehyde with an amino group to form anils



METHOD OF ASSAY

The method of determination of free sulfapyridine and total sulfapyridine throughout this report is that of Marshall and Biatton² However, some precautions were necessary because of the tendency of the glucose sulfapyridine complex to hydrolyze rapidly on acidification For the analysis of free sulfapyridine in glucose-sulfapyridine, the procedure must be done immediately after the bleeding or the blood sample must be kept in the chill room until analyzed The determination in the trichloroacetic acid filtrates must be done immediately after the precipitation and filtration are complete If allowed to stand for any length of time, the acid medium is optimal for liberation of free sulfapyridine from the glucose-sulfapyridine complex If the determinations are done at once, time and temperature will not have been able to play any rôle or to affect hydrolysis The value obtained for free sulfapyridine, in this technic, will be the free sulfapyridine present in the blood stream when the sample was taken The total sulfapyridine value obtained will consist of free sulfapyridine, complex sulfapyridine (glucose-anil) and acetylated sulfapyridine

ANIMAL EXPERIMENTS

In order to determine the comparative therapeutic effect of glucose sulfapyridine and ordinary sulfapyridine, mouse protection studies were undertaken In a series of tests involving the oral use of glucose sulfapyridine in 35 mice, and of equal amounts of a sulfapyridine suspension (with a small amount of gum acacia added to maintain a homologous mixture) in 35 other mice, no essential difference in toxicity or survival rates between the two drugs was noted In the animals which died toxicity due to drug was differentiated from pneumonia by the presence of hematuria in the animal when alive, and the absence of pneumococci in the heart's blood when autopsied In these experiments, the therapeutic dose of glucose sulfapyridine was so near the toxic dose that the therapeutic effect was masked With a dose of 2 gm per kilo per day of either drug, protection against 200 M F D of virulent Type II pneumococci is approximately 70 per cent

The relative absorption of equal amounts of sulfapyridine and of the sulfapyridine suspension given orally was studied in a group of 12 rabbits When fed either 100 mg or 300 mg per kg body weight of these drugs, the rabbits which received the glucose sulfapyridine showed the higher blood levels, this difference was more marked with the larger of the two doses used The rapidity of absorption was about the same These results are at variance with those obtained with patients treated with equal amounts of the two drugs It was found that gum acacia did not influence the rate of absorption in the sulfapyridine suspension, and when absorption and protection tests were done on a group of 24 rats, results similar to those obtained with rabbits were observed

HUMAN ABSORPTION OF GLUCOSE-SULFAPYRIDINE

The absorption of glucose-sulfapyridine (10 per cent sulfapyridine in 50 per cent glucose) when administered to humans orally, intravenously, and by rectum has been studied. Frequent blood samples were taken from selected patients who received the drug by the various routes, and daily specimens were obtained from nearly all of the 130 patients with pneumonia who were treated with glucose-sulfapyridine by mouth. These oral results are to be compared with those obtained when sulfapyridine tablets are administered.

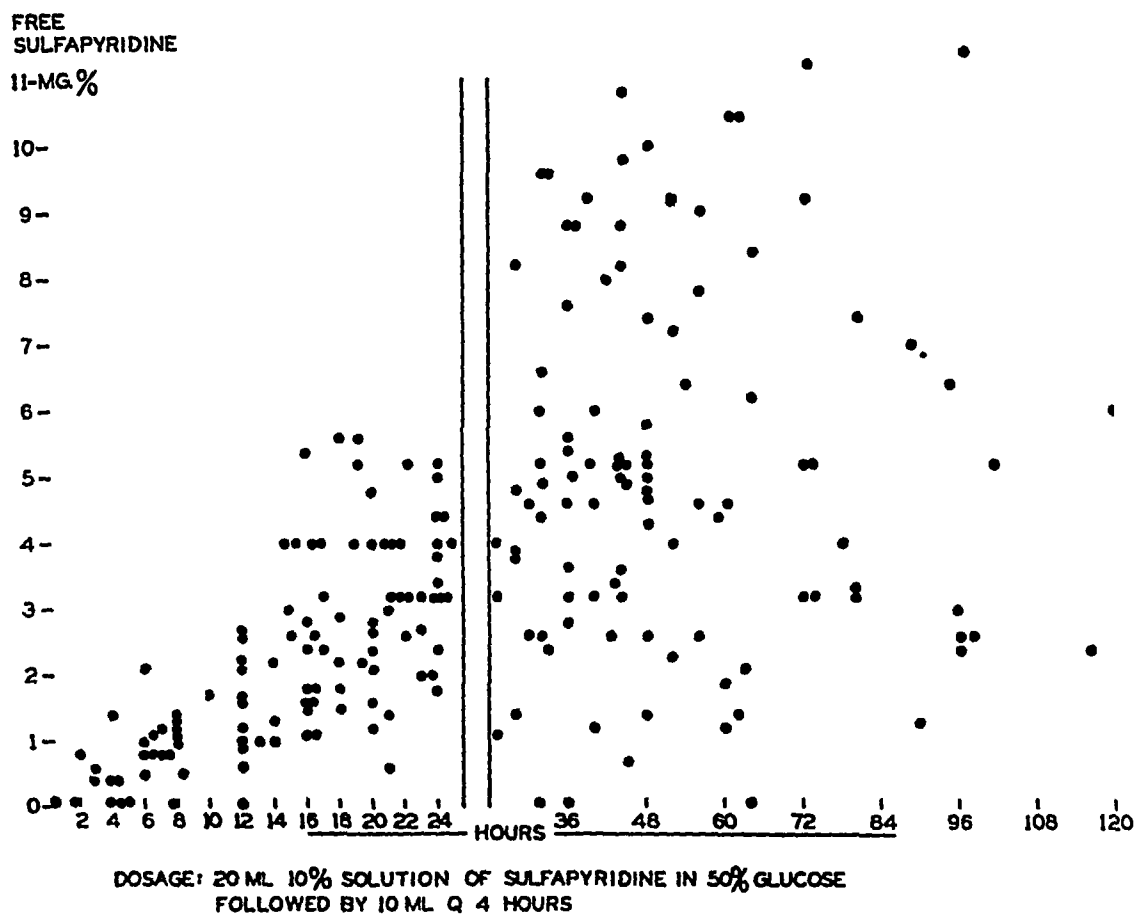


FIG 1 Blood levels of free sulfapyridine after oral administration of glucose sulfapyridine

Oral Administration When glucose-sulfapyridine is given by mouth in the dosage of 2 gm (20 c c of solution) followed by 1 gm every 4 hours, the blood sulfapyridine content rises slowly but steadily for about 24 hours (figure 1). After this the absorption curve tends to level off, although as this dosage is continued, the content increases somewhat over the next 24 or 48 hours in many patients. These findings confirm those of Finland and his associates.^{7, 8}

When sulfapyridine tablets are administered in the same dosage, the blood sulfapyridine content rises more rapidly, and the absorption curve tends to level off after about 12 hours, increases after this time come more slowly.

The average maximum blood sulfapyridine level obtained by the oral administration of these two compounds is about the same, the difference lies in the speed of their attainment

In experiments concerning the anti-pneumococcal power of blood of patients receiving glucose-sulfapyridine by mouth, Finland and his associates have found that the bacteriostatic and bactericidal power of such blood is equivalent, level for level, to blood of patients receiving the ordinary sulfapyridine tablets

10-MG. %

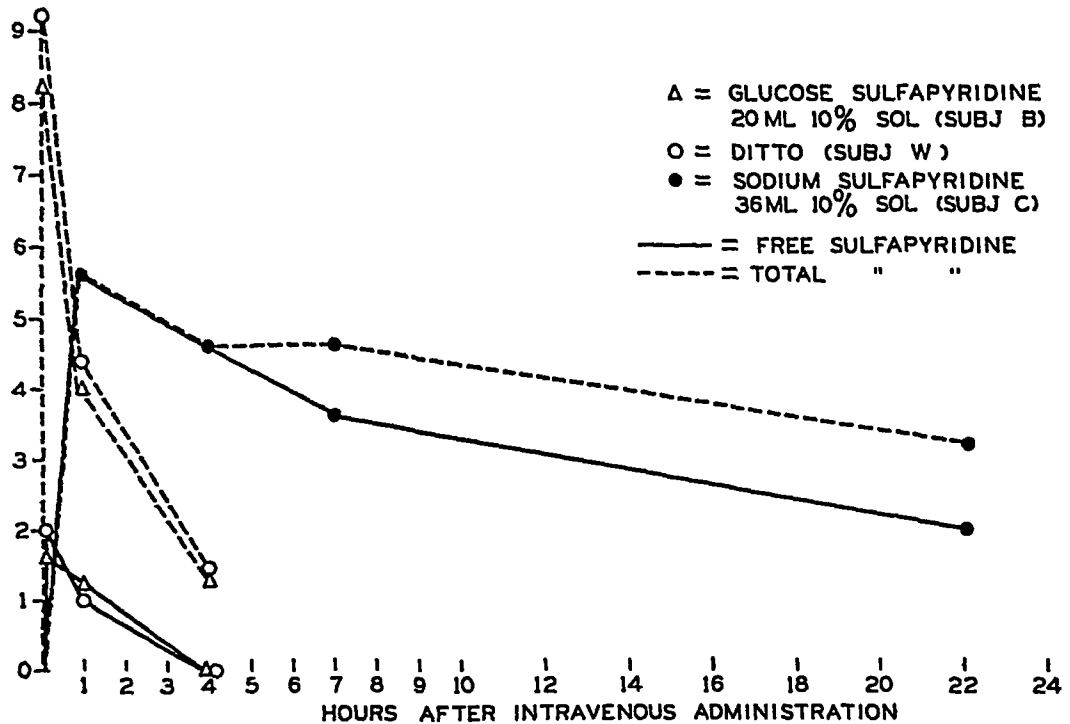


FIG 2 Blood levels of free and total sulfapyridine after intravenous administration of glucose sulfapyridine compared with sodium sulfapyridine

Intravenous Administration The production of a soluble form of sulfapyridine which is not highly alkaline (as is sodium sulfapyridine, whose pH is about 11), led to the hope that the new preparation would be suitable and safe for parenteral use when indicated. Preliminary studies were first made regarding the blood levels which might be obtained after intravenous injection before using the drug by this route in pneumonia patients.

Twenty c.c. of the undiluted glucose-sulfapyridine preparation were administered slowly (2 to 3 c.c. per minute) to six selected patients on the medical wards. Patients with known kidney damage were not used, since excretion of sulfapyridine may be delayed in such patients. Frequent blood samples were taken for study.

The blood sulfapyridine content naturally rose quite rapidly (figure 2)

Three to five minutes after the completion of the injection, the total sulfapyridine content of the blood varied from 8 to 12 mg per cent. The free sulfapyridine content at this time was low, however, varying from 1 to 2 mg per cent. This shows that the glucose-sulfapyridine is not hydrolysed to free sulfapyridine in the blood stream. The level of both free and total sulfapyridine fell rapidly after injection, and at the end of four hours only traces of free drug and 1 to 2 mg per cent of "total" drug remain in the blood stream. This rapid fall is due to the fact that the injected drug is excreted rapidly in the urine.

Finland and his associates³ have reported similar findings when glucose-sulfapyridine is injected by vein in a more dilute solution. Their results differ from ours, however, in the comparative amounts of free and total drug recovered from the blood stream, the free drug apparently accounting for about 50 per cent of the total in their experiments and only 15 to 20 per cent in ours. This difference may be due to differences in method and time of assay. After intravenous administration of the glucose-sulfapyridine compound, three derivatives are found in the blood. These are (1) free sulfapyridine (since about 10 per cent of the material before administration is in the free form), (2) the glucose-anil, and (3) acetylated sulfapyridine. With the modification of Marshall's method which we use, the latter two compounds are indistinguishable under the ordinary conditions under which the estimations were carried out. The value for free sulfapyridine, on the other hand, seems to be readily estimated separately. Finland and his associates believe, however, that the free sulfapyridine and the glucose-anil test as one and the same drug under conditions prevailing in their laboratory. This probably accounts for the difference in comparative amounts of free and "total" drug which are obtained in the two laboratories. From a practical point of view our results are in agreement as to the fact that the blood level falls too rapidly after intravenous administration of glucose-sulfapyridine to make this route of injection of value. In addition, Finland's group has shown that the blood of patients who receive the glucose-sulfapyridine intravenously does not have anti-pneumococcal power.⁵

Administration by Rectum Four patients were given cleansing enemas followed by retention enemas of glucose-sulfapyridine in 200 to 300 c c of tap water. Two patients were given 20 c c of the compound, one patient 30 c c and one patient 40 c c. The tap was well retained in each case. Blood specimens were obtained 45 minutes after administration of the drug and again 24 hours later. The blood showed only traces of free drug and values of "total" drug ranging from traces to 0.8 mg per cent, the latter figure was obtained when 40 c c of the compound were administered.

CLINICAL RESULTS

Since October 1938 a study of the chemotherapy of pneumonia has been in progress at Bellevue Hospital. Glucose-sulfapyridine has been one of the

chemotherapeutic agents under investigation. Although it soon became evident that this preparation would not be useful for intravenous injection, it was decided to ascertain its possible value as an oral medicament. While it is possible to crush sulfapyridine tablets and suspend them in milk or water, in our experience a goodly amount of the drug was likely to remain in the bottom of the medicine glass. A soluble non-irritant preparation such as glucose-sulfapyridine would obviate this difficulty.

During the period of investigation, 130 cases of pneumonia have been treated with glucose-sulfapyridine orally. Certain wards were set aside and all pneumonia patients entering these wards were treated with this preparation. The cases which form the material of this clinical report were, therefore, unselected. No case was included which had not either frank physical or roentgen-ray evidence of pneumonia.

On admission of each case, a blood culture was taken before treatment and subsequent cultures were done, if fever persisted. Treatment with sulfapyridine was started as soon as the clinical diagnosis had been made and blood and sputum collected for bacteriological examination. In each case the sputum was typed as soon as feasible, directly if possible, and in each case mouse typing was also done.

Thirty-two of the 130 cases received serum. The serum treated cases were not selected because of failure to respond to sulfapyridine, but because they were part of a larger alternated series of cases that,⁶ on rotation by type, were due to receive serum plus sulfapyridine rather than sulfapyridine alone. Some cases due to receive serum in the alternated series did not receive it because recovery on sulfapyridine alone was obvious by the time a typing was obtained. Four cases of probable pneumococcus endocarditis (three of whom had had good initial responses to glucose-sulfapyridine) received, without effect, sodium sulfapyridine later during their course, and five other cases received initial doses of 1 to 2 gm of sodium sulfapyridine. Sixty-five cases were under 50 years of age and 65 were 50 or over.

RESULTS

The results in terms of mortality are shown in table 1. It will be seen that there were 127 cases of pneumococcus pneumonia and three cases of Friedlander's pneumonia. In the pneumococcus pneumonias there were 18 deaths with a gross mortality of 14 per cent. If six cases in which death occurred in less than 24 hours after admission are excluded the mortality is 9.9 per cent.

If the group of bacteremias is analyzed separately the results are 12 deaths (55 per cent) in the 22 bacteremic cases. If three 24 hour deaths are excluded, there were 9 deaths in 19 cases (47 per cent).

There were two cases of Type B Friedlander's pneumonia, one of them bacteremic. Both recovered from their pneumonia, but one who had had edema and ascites on admission died afebrile three months after admission of

TABLE I
Distribution of Cases and Mortality Rates by Types

Type	Non-Bacteremic		Bacteremic		Total	
	Cases	Deaths	Cases	Deaths	Cases	Deaths
Pneumococcus Cases						
I	15	1	4	1	19	2
II	15	1	4	3	19	4
III	9	1	3	2	12	3
IV	5	0	0	0	5	0
V	9	0	1	0	10	0
VI	1	0	0	0	1	0
VII	16	2	3	2	19	4
VIII	10	0	2	0	12	0
X	3	0	0	0	3	0
XI	2	1	0	0	2	1
XII	1	0	0	0	1	0
XIII	1	0	0	0	1	0
XIV	0	0	1	1	1	1
XV	2	0	0	0	2	0
XVII	2	0	0	0	2	0
XVIII	0	0	1	1	1	1
XIX	5	0	1	1	6	1
XX	0	0	1	1	1	1
XXI	1	0	0	0	1	0
XXIV	2	0	0	0	2	0
XXV	1	0	0	0	1	0
XXIX	3	0	1	0	4	0
XXXII	2	0	0	0	2	0
Totals	105	6 (5.7%)	22	12 (55%)	127	18 (14%)
Excluding 24 hr deaths	102	3 (2.9%)	19	9 (47%)	121	12 (9.9%)
Friedlander Cases						
A	1	1	0	0	1	1
B	1	0	1	1	2	1

cirrhosis of the liver One case of Type A Friedlander's pneumonia (non-bacteremic) died one week after admission

Complications There were four cases of probable pneumococcus endocarditis with persistent bacteremia and development of cardiac murmurs (unfortunately none with autopsy), three of meningitis (one with recovery), two of grossly purulent empyema with recovery without thoracotomy on needle aspiration only, three of serous effusion who recovered with aspiration only, and two cases of otitis media

DISCUSSION

We have noted only slight differences in the clinical effect of glucose-sulfapyridine and sulfapyridine tablets in the oral chemotherapy of pneumonia. The gross mortality rate of 14 per cent in these glucose-sulfapyridine treated pneumonias is about identical with the mortality rate (15 per cent) of a similar series of sulfapyridine treated cases reported from Bellevue

hospital by our group. However, the results in the bacteremic cases are not as good. In the sulfapyridine series there were 35 bacteremic cases, of whom 12 died (34.3 per cent), excluding 24 hour deaths there were only 8 deaths (25.8 per cent). While the total number of bacteremic cases in each series is not large, the fact remains that the mortality rate with glucose-sulfapyridine was much higher (55 per cent for all cases, 47 per cent if 24 hour deaths are excluded). Since it is of course not possible to determine immediately which cases are bacteremic, the glucose-sulfapyridine, while apparently adequate for most non-bacteremic cases, is not to be recommended.

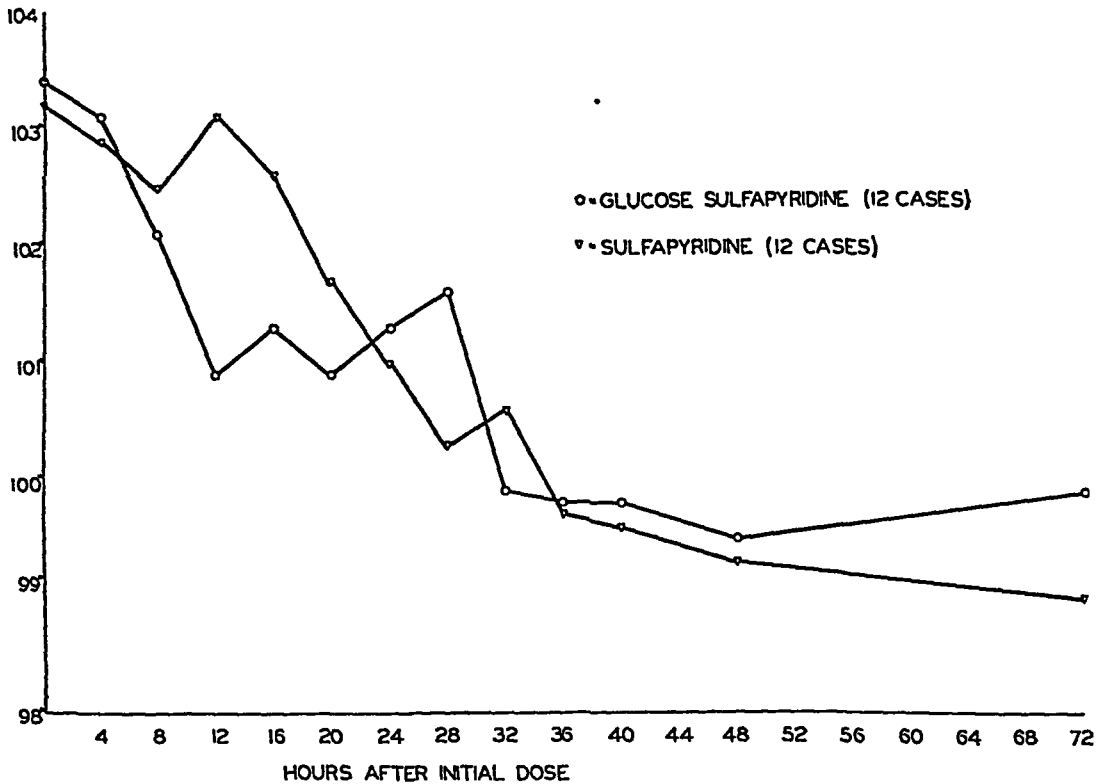


FIG 3 Average temperature curves

as a preparation for routine use in pneumonia. It is likely that prompt establishment of "adequate" blood levels (just what constitutes adequate levels is still not decided) is necessary in order to save the largest possible number of the seriously ill patients.

The effect on the temperature curve is essentially the same as can be seen from figure 3, which shows composite temperature curves of 12 cases (six Type I and six Type VII) treated with glucose-sulfapyridine, and 12 cases of the same types treated with sulfapyridine tablets in the same hourly dosage. These cases were the first six in each Type I and Type VII group who fell by lot into the "drug only" series for treatment by the respective agent.

There was only one case of granulocytopenia (with recovery), two mild secondary anemias, one case of gross hematuria and renal colic, and two cases of psychosis (which cleared when the drug was discontinued), and one case

of cyanosis ascribable to sulfapyridine. Nausea and vomiting seemed to be less frequent with glucose-sulfapyridine than with plain sulfapyridine tablets. Of the 130 cases 49 (38 per cent) had either nausea or nausea and vomiting. Of these 49, nine had nausea only, and of the 40 who had vomiting, this was classified as severe in seven, moderate in 24, and slight in nine cases. This figure of 38 per cent is significantly lower than the 52 per cent of nausea and vomiting in the series of sulfapyridine treated cases previously reported. We attribute this lowered incidence of nausea and vomiting to the slower rise of the absorption curve of glucose-sulfapyridine.

It is interesting to note that not only did we not infrequently see dramatic and critical falls in temperature with blood levels of less than 4 mg per cent, but also the composite temperature curve is essentially the same as that of tablet treated cases with a more rapid rise of blood sulfapyridine.

CONCLUSIONS

1 A concentrated (10 per cent) solution of sulfapyridine has been prepared in combination with glucose, yielding what is believed to be a glucose-anil.

2 When this solution is administered orally to rats and rabbits, a higher blood level of both free and "total" sulfapyridine is obtained than with an equal amount of free sulfapyridine in suspension.

3 When 2 gm per kilo per day of either glucose-sulfapyridine or sulfapyridine suspension are fed to mice, protection against 200 M F D of virulent Type II pneumococci is approximately 70 per cent.

4 Oral administration to humans results in a delayed absorption into the blood stream, the blood curve level rising slowly for about 24 hours and then tending to level off. The relative percentage of free and total sulfapyridine in the blood stream is in the same general range obtained when ordinary sulfapyridine is given. With the latter drug absorption is more rapid.

5 Intravenous administration to humans of 20 c c of the glucose-sulfapyridine solution results in an immediate high level of "total" sulfapyridine but a low level (1 to 2 mg per cent) of the free drug. Both of these levels fall very rapidly.

6 Rectal administration to humans of glucose-sulfapyridine is followed by very little absorption.

7 Only slight differences in the clinical effects of glucose-sulfapyridine and sulfapyridine tablets have been noted, and the gross mortality in the two groups is about the same. In the bacteremic cases, however, there is a distinctly higher fatality rate in the glucose-sulfapyridine group. Since it is not possible immediately to determine which patients have bacteremia, glucose-sulfapyridine is not recommended as a preparation for routine use in pneumonia.

Mr. Frank B. Ablondi performed many of the animal experiments and chemical determinations.

DEATHS

Name	Age	Type	Total Drug Gm	Units Serum	Remarks
W P	54	I	145	0	Diabetes mellitus Bacteremia on admission and persistently from 3rd week until death from pneumococcus endocarditis on 56th day No response to either sodium sulfapyridine or sulfathiazole
L B	60	I	4	0	24-hour non-bacteremic death
P P	55	II	6	330 000	4 gm glucose-sulfapyridine and 2 gm sodium sulfapyridine I V Died 13½ hours after admission
J F	60	II	42	170 000	Bacteremia 500 colonies per c c on admission Temporary sterilization of blood stream but recurrence of bacteremia persisting in spite of sodium sulfapyridine by mouth and by vein Died of pneumococcus endocarditis and meningitis 3 weeks after admission
J S	57	II	18	0	Overwhelming bacteremia with innumerable colonies Died 4th day
R W	53	II	31	0	Bacteremia 58 and 89 colonies per c c Blood stream never sterilized in spite of levels of 4 to 9 mg % (also received sodium sulfapyridine) Probable endocarditis Died 6th hospital day
C V	70	III	5	0	Admitted late in disease Bacteremia 18-hour death
R B	64	III	32	360 000	Bacteremia 22 colonies per c c Arteriosclerotic heart disease with decompensation on admission Died 6th hospital day with normal temperature
J B	62	III	12	0	No response to drug in spite of good levels At autopsy showed consolidation of RLL, LLL, and partial consolidation of RUL and LUL
P F	46	VII	48	0	Bacteremia 7 and 17 colonies per c c Sterile at 96 hours but recurrence and persistence of bacteremia after 11th day in spite of glucose and sodium sulfapyridine Developed aortic diastolic murmur and died one month after admission of pneumococcus endocarditis
J O	52	VII	24	0	Myeloblastic leukemia with 530,000 W B C and 97% myeloblasts on admission Consolidation RUL, RLL, LLL Died on 3rd hospital day
W L	56	VII	8	400 000	Four day history of pneumonia beginning during alcoholic bout Jaundiced on admission with consolidation of 3 lobes Bacteremia 100 and 150 colonies per c c Died 45 hours after admission Autopsy
W P	55	VII	2	0	Admitted 6th day of disease, moribund, in pulmonary edema Died 8½ hours after admission
J O	66	XI	34	120 000	Admitted in diabetic acidosis which was easily controlled Initial good response but relapsed on 5th hospital day and died on 10th day
H B	65	XIV	4	0	Bacteremia 121 and 75 colonies per c c Died 18½ hours after admission
W P	54	XVIII	26	0	Elderly hypertensive admitted on 6th day of disease with bacteremia, 150 colonies per c c Blood cultures persistently positive Died with meningitis on 6th hospital day

DEATHS—*Continued*

Name	Age	Type	Total Drug Gm	Units Serum	Remarks
C J	67	XIX	2	0	Two previous admissions for arteriosclerotic heart disease with decompensation Admitted in frank failure, with bacteremia 30 and 34 colonies per c c Died 16 hours
A A	54	XX	18	200 000	Bacteremia with innumerable colonies on admission Subsequent blood cultures sterile but no temperature response Died 4th hospital day Autopsy Confluent lobular pneumonia entire right lung Empyema, right Arteriosclerotic heart disease with decompensation
F F	74	Fried A	50		Type XXI in sputum Friedlander Group A empyema
J M	41	Fried B	60	0	Angiomata of face and thorax and history of pancreatitis 10 years previously Consolidation RUL and bacteremia Developed lung abscess one month after admission which healed by time of death, 2 months later Jaundice present on 7th hospital day, edema and ascites on 13th hospital day Repeated paracentesis Afebrile death, probably from cirrhosis of the liver

BIBLIOGRAPHY

- 1 BLAKE, F G, and HAVILAND, J W Sulfapyridine in pneumococcal, streptococcal and staphylococcal infections, *Internat Clin*, 1939, iv, 1
- 2 BRATTON, A C, and MARSHALL, E K, JR New coupling component for sulfanilamide determination, *Jr Biol Chem*, 1939, cxxviii, 537
- 3 TAYLOR, F H L, LOWELL, F C, ADAMS, M A, SPRING, W C, JR, and FINLAND, MAXWELL A comparative study of the blood concentrations and urinary excretion of sulfapyridine and sulfanilamide after single doses of compounds administered by various routes, *Jr Clin Invest*, 1940, xix, 201
- 4 FINLAND, MAXWELL, LOWELL, F C, SPRING, W C, JR, and TAYLOR, F H L Parenteral sulfapyridine, the intravenous use of sodium sulfapyridine and a report of clinical and laboratory observations on the use of a glucose-sulfapyridine solution, *ANN INT MED*, 1940, viii, 1105
- 5 LOWELL, F C, SPRING, W C, JR, and FINLAND, MAXWELL Bactericidal action of sodium sulfapyridine and of a glucose-sulfapyridine solution in human blood, *Jr Clin Invest*, 1940, xix, 215
- 6 PLUMMER, NORMAN, LIEBMANN, JAMES, SOLOMON, SALL, KAMMERER, W H, KALKSTEIN, MENASCH, and ENSWORTH, H K. Chemotherapy versus combined chemotherapy and serum in the treatment of pneumonia, *Jr Am Med Assoc*, 1941, cxvi, 2366

A SYNDROME OF UPPER ESOPHAGEAL STENOSIS^{*}

By MORTIMER R CAMHI, M D, and LEO LOEWE, M D,
Brooklyn, New York

STARVATION overshadows the many other sequelae of esophageal stenosis. Pulmonary complications, for instance, unless of calamitous proportion, are often overlooked or misinterpreted. Attention is usually directed to the more dramatic accidents such as perforation into the trachea. The more frequent complications are either insufficiently emphasized or not widely appreciated. With certain types of esophageal stenosis these may occur with such constancy as to become part of the clinical syndrome.

This report concerns itself with the syndrome of aspiration of ingesta into the air passages due to esophageal stenosis. Following a review of our clinical material we felt the need for further elucidation of the symptomatology and the mechanism of the clinical picture. A plausible anatomical and physiological explanation is offered to explain the succession of events.

A brief review of the literature corroborated our impression that the origin of the pulmonary complications has received relatively little attention. McCrae¹ stated that dyspnea could be a prominent feature of carcinoma of the esophagus, even before dysphagia, if either or both of the recurrent laryngeal nerves become involved. Jackson, Tucker, and Clerf² found that cough may be brought on by an overflow of food and secretion from the esophagus into the larynx. Likewise, esophageal paralysis seriously interferes with swallowing. The pyriform sinuses fill and overflow into the larynx (Chevalier Jackson sign of esophageal stenosis)³. Jackson and Jackson⁴ were so impressed with the frequent oversight of the esophageal origin of pulmonary symptoms that they discussed, in a separate communication, the many ways in which this can occur. They cite aspiration of ingesta as a cause. They have had the experience that any stenosing lesion, by causing an overflow of the esophageal contents, may result in contamination of the tracheo-bronchial system. They have observed overflow with the following esophageal lesions: congenital stenosis, foreign bodies, syphilis, aneurysm, cardiospasm, and benign and malignant new growths. Recurrent laryngeal nerve involvement is also listed as a cause for aspiration. They do not mention having actually seen the overflow during a fluoroscopic examination, but have come to their conclusion from highly presumptive evidence. Vinson and Kimmelsteil⁵ believe that regurgitation of mucus is inevitable in any case of complete obstruction of the esophagus. When this occurs at night, it is associated with aspiration and may lead to chronic bronchiectasis. They have noted aspiration as a complication of cardiospasm. Vinson⁶ believes

^{*} Received for publication July 5, 1940.

From the Brooklyn Cancer Institute, Brooklyn, New York, Division of Cancer, Maurice Lenz, M D, director, Department of Hospitals, New York City.

that every esophageal history should include inquiry concerning regurgitation, and whether or not this is associated with strangling as a result of aspiration into the air passages. He believes that aspiration may take place from any esophageal stenosis. However, he states⁷ that "respiratory symptoms are less frequent in carcinomatous obstruction than in that from other esophageal lesions, unless the growth has penetrated the wall of the trachea or a bronchus with formation of a fistula." This last is at variance with our experience.

Mathews and Schnabel⁸ investigated 108 autopsied cases of carcinoma of the esophagus. Eighty-six were of the stenosing variety, 22 of the non-stenosing type. Every lesion in the uppermost third of the esophagus was of the stenosing type. The part pneumonia played in the termination of life in the stenosing group assumed great importance, 67 per cent of this series dying from this immediate cause. The authors believe that at least some of the pneumonias were due to the aspiration of food. Keefer⁹ described 17 cases of esophageal carcinoma accompanied by serious pulmonary complications. Twelve of these were caused by perforation of the cancer, only one by aspiration of ingesta into the tracheobronchial tree. He states therefore, that the majority of such pulmonary complications are usually the result of perforation into the trachea, bronchi, mediastinum, lung, or pleura. However, since he presents a highly selected group of cases, most of which perforated, we cannot conclude that in an unselected series this would be the usual mechanism of pulmonary involvement. Rastelli¹⁰ described an interesting case of malignant stenosis at the upper end of the esophagus. His patient complained of hoarseness, cough, and dysphagia. He was emaciated, and had râles and dullness at both lung bases. The fingers were clubbed. Roentgen-ray examination of the lungs disclosed areas of increased density in the right middle and lower, and in the left lower lobes of the lung. The diagnosis was bronchopneumonia. On fluoroscopic study of the esophagus the barium was held up at the site of the lesion and then spilled over the top of the esophagus into the larynx and tracheo-bronchial tree. The right recurrent laryngeal nerve was involved causing a fixed right vocal cord. He believed that since the cords could not approximate in the midline, the ingesta had an unimpeded passage into the lung, thereby causing aspiration pneumonia.

Jousseau¹¹ classifies the respiratory symptoms as laryngotracheal or pulmonary in origin. He agrees with Collet, whom he quotes, in stressing the frequent involvement of the recurrent laryngeal nerve as a factor in the production of respiratory symptoms such as hoarseness, aphonia, or stridor. He also states that bulging or fistula into the tracheo-bronchial tree may be responsible for these symptoms. However, he does not mention aspiration as a prominent cause of respiratory complaints.

In contradistinction to Jousseau, Collet, and others who believe that the recurrent laryngeal nerve involvement is frequent with carcinoma of the esophagus, Vinson¹² in discussing his studies of 1,000 cases of esophageal

malignancy, cites only 17 instances of paralysis of one or both cords. These cases were seen in a large clinic between 1923 and 1933 and it is possible that since the involvement was not suspected, it was not sought for in each case. In a later discussion⁶ the same author aptly warns that hoarseness associated with difficulty in swallowing, should suggest an esophageal lesion of malignant type.

The 30 cases which comprise this study were culled from the files of the Brooklyn Cancer Institute. However, the diagnosis of carcinoma could not be verified in each instance. Common to all was obstruction in varying degree of some part of the esophagus. Roentgen-ray and fluoroscopic examinations* of the esophagus were performed in every case. Wherever possible esophagoscopy† and roentgen-ray of the chest were also done. cursory correlation of the pulmonary complications with the esophageal lesions led us to believe that the incidence of lung affections was greatest when the esophagus was involved in its uppermost third. The cases were then arbitrarily classified as to their location in the upper third or lower two-thirds of the esophagus. Thereafter the cases were unselected, being entered on the chart in sequence according to the patient's date of application to the clinic.

We then studied the age and sex of the patient, the type and duration of complaint, the roentgen-ray and fluoroscopic findings in the esophagus, the presence of aspiration into the tracheo-bronchial tree, the condition of the esophagus as seen by esophagoscopy, the location of the lesion, the presence or absence of vocal cord paralysis, whenever possible, the pathology of the lesion, the roentgen-ray and clinical findings in the chest, the presence of clubbing of the fingers, and finally, the course and outcome of the disease.

ANALYSIS OF THE LESIONS WHICH INVOLVED THE UPPERMOST THIRD OF THE ESOPHAGUS (CHART 1)

Thirteen cases, or 43.3 per cent of the total, showed involvement of the uppermost third of the esophagus. In two instances (cases 3 and 5) this involvement was secondary to lesions proximal to it. The sex incidence was as expected, there being only one female in the group. The average age was 58 plus years. The most common complaint was inability to swallow properly, but cough, hoarseness, vomiting, pain, and cervical mass were also observed. The average duration of complaints before a physician was consulted was approximately five and a half months.

Radiographic studies of the esophagus showed it to be involved primarily or secondarily in every case. Fluoroscopic examination with barium gave extremely important information. The degree of difficulty in swallowing could be visualized. More significant, the actual welling over of barium from the esophagus into the trachea could be demonstrated. This was ob-

* We wish to thank Dr. S. W. Westing, roentgenologist, for his helpful cooperation.

† Likewise, we thank Dr. M. E. Myerson and Dr. Jas. Schmidt on whose services the esophagoscopies were done.

CHART I

Analysis of Lesions in Upper Third of Esophagus

The Cases are Unselected, Being Entered on Chart in Succession According to Date Admitted

Case No.	Sex	Age	Duration in Months	Roentgen-Ray and Fluoroscopic Examination of Esophagus	Aspiration	Esophagoscopy	Location of Lesion	Vocal Cord Status	Biopsy of Lesion	Chest Examination	Clubbing of Fingers	Course and Comment
1000	M	33	3	9/27/37—Swallows with greatest difficulty. Lumen of esophagus narrowed to 1/4" at cricoid level. There is long retention and delay of barium	After several forceful acts of swallowing the barium spills over into trachea	9/30/37—An irregular superficial mass protruded into esophagus from left anterior cricopharyngeus wall	Uppermost portion of esophagus	Not noted	No evidence of malignancy	10/4/37—No evidence of pulmonary, pleural, or mediastinal affection aside from barium in tracheo-bronchial tree	Present	Received roentgen therapy to the esophagus. Subsequent esophagoscopy and roentgen-ray studies reveal only scarring. Malignancy not proved. Clubbed fingers still present. Undiagnosed low grade pneumonitis due to aspiration probably accounts for clubbing
1001	M	58	7	11/16/37—There is a constant circular constriction at the level of the cricoid. 2/23/38—No swallowing difficulty. 3/30/38—Greatest swallowing difficulty	3/30/38—A few drops of barium enter tracheobronchial tree by spilling over	11/23/37—A cauliflower infiltrative lesion 18 cm from the incisors is present on the anterior cricopharyngeus wall	Uppermost portion of esophagus	Both cords paralyzed in parallel position 1/25/38	Squamous cell ca	11/15/37—Roentgen-ray chest negative. 2/23/38—Roentgen-ray chest negative. 4/20/38—Bronchopneumonic affection of right upper two-thirds of lung (mild). Physical findings those of severe bronchopneumonia	Absent	Gastrostomy done but patient died 4/20/38 of aspiration bronchopneumonia
1002	M	67	6	11/23/37—An irregular filling defect is noted at the junction of the hypopharynx and esophagus. Swallows with greatest difficulty and pushes food down slowly	A small quantity of barium is spilled over into the air passages	1/11/38—There is an induration of the right aryepiglottic fold and arytenoid extending into right pyriform fossa	Junction hypopharynx and esophagus	Right cord paralyzed	Epidermoid ca	11/23/37—Obliterated costophrenic angle. 1/11/38—Some emphysema present. Developed aspiration bronchopneumonia before death	Not noted	Died 5/1/38 of aspiration and terminal pneumonia

S 4 24/38	M 47	Dysphagia	4	1/27/38—Very irregular filling defect on the posterior wall of the esophagus in its cervical portion above the clavicles Epiglottis lacks function and there is great swallowing difficulty	Barium spills over into the right air passages	2/3/38—Granulation present on posterior surface of arytenoid extending into esophagus marking opening of the cricopharyngeus a hazardous procedure	Upper-most portion of esophagus	Right cord paralyzed	Squamous cell ca	1/27/38—Bronchopneumonic consolidation of right lower two thirds apparent due to inspiration of food Thickened bilateral apical pleura 3/1/38—Above process more advanced Additional lobes involved 3/30/38—Bronchopneumonic process shows signs of clearing up (post-gastrostomy)	Present	Patient became extremely emaciated Bronchopneumonia due to aspiration cleared up somewhat following gastrostomy but the patient went downhill Later the isolated from incision and drainage of neck abscess Died 1/19/38
W 5 25/38	M 60	Mass in neck	4	10/31/38—The lumen of the esophagus is narrowed to $\frac{1}{8}$ " at a point 15 cm below incisors just below base of larynx The narrowed area is extremely irregular in outline There is considerable obstruction above this point	No barium noted in tracheo-bronchial tree on single examination which was done Later developed marked swallowing difficulty	5/9/38—No laryngeal pathology noted Esophgroscope passed with difficulty There is a deformity at the upper end of the esophagus pushing the posterior wall forward Possibly enlarged glands 11/1/38—Friable mass found in right pyriform fossa	Upper-most portion compressed	No paralysis present	Squamous cell ca	1/25/38—No osseous or pulmonary pathology noted on chest plate 8/22/38—Small pleural effusion right base Thickening of the pulmonary markings, especially at the right base 1/1/39—Coarse motting lower two-thirds right lobe Extensive bronchopneumonia	Present	The first portion of the esophagus was compressed Only one examination done early in condition, no aspiration was noted, but he later developed great difficulty in swallowing and clinically is said to have died from aspiration bronchopneumonia 1/8/39
D 6 23/38	M 52	Hoarseness Dysphagia	6 2	9/26/38—20 cm below incisors is a concentric constriction extending for 5 cm 10/20/38—During fluoroscopic examination for localization of lesion for deep therapy department, some barium entered trachea	9/26/38—No barium enters air passages 10/20/38—Barium spilled over into right main bronchus	9/29/38—Edema present in arytenoid region Considerable mucus present No evidence of any post-cricoid or laryngeal lesion About 2 cm below crico-pharyngeus, a large, granular, bleeding mass fills almost entire upper esophagus Tracheal examination reveals lesion in lateral tracheal wall	Upper esophagus 2 cm below cricopharyngeus	Paresis left cord	Squamous cell ca in esophagus and trachea	9/20/38—Fibrotic changes are noted in the base of the right lung field 10/25/38—Small areas of bronchopneumonic affection just above the right half of the diaphragm These seen 9/20/38 called fibrotic changes are probably due to aspiration Barium disappeared from air passages	Absent	Had a gastrostomy but tried to take fluid by mouth and developed aspiration bronchopneumonia Developed cough with thick yellow brown sputum Died 11/17/38

CHART I (Continued)

Case No.	Age	Chief Complaint	Duration in Months	Röntgen-Ray and Fluoroscopic Examination of Esophagus	Aspiration	Esophagoscopy	Location of Lesion	Vocal Cord Status	Biopsy of Lesion	Chest Examination	Clubbing of Fingers	Course and Comment
77	61	Dysphagia Hematemesis	5	10/3/38—At level of clavicles the esophagus shows a forward bulging with greatly disturbed mucosal pattern. There is no appreciable obstruction but a markedly disturbed swallowing mechanism.	10/3/39—With every act of swallowing, some brim spills over into tracheo-bronchial tree.	10/18/38—Lesion found on posterior esophageal wall at entrance to the esophagus. Both cords fixed leaving a chunk for respiration.	Entrance to esophagus	Both paralyzed	Acanthosis	10/3/38—Cherry sized area of bronchopneumonia 1" above rt diaphragm. 10/24/38—Rt lung less illuminated than left suggesting moderate atelectasis. Evidence of pn or bronchopn cannot be detected. 10/29/38—Both lower thirds show considerable mottling due to bronchopneumonia.	Beginning	Patient developed a marked stridor because both cords were paralyzed. Developed an aspiration bronchopn and died 11/1/38.
78	63	Dysphagia Hematemesis	3	10/17/39—Mucosa greatly disturbed and lumen greatly narrowed for 3-7 cm at level of the sixth cervical vertebra. Food passage markedly delayed.	10/17/38—Not seen. Only one examination done.	10/18/38—Right cord fixed. Only slight motility of left. Marked spasm and cyanosis of patient did not allow passage of esophagoscope during cervical anesthesia.	Upper esophagus	Right paralyzed Left paresis	Not obtained	10/17/38—Rt costophrenic angle obliterated by adhesions. 12/6/38—Trachea narrowed to less than finger width. Marked bulging into right lung field apparently due to swelling of mediastinal structures. 1/13/39—Bronchopn both bases.	Absent	Had tracheotomy and gastrostomy but died of bronchopneumonia 1/15/39. General anesthetic no longer given to esophagus patients before careful vocal cord examination.
79	66	Dysphagia Hematemesis	1	11/3/39—At level of lower surface of the clavicles, the lumen is narrowed to 0.6 cm for distance of 5.0 cm. Mucosal pattern destroyed with formation of a pea sized crater from the involved area. A streak of brim extends into trachea. Swallowing difficult but not delayed.	Esophago-tracheal fistula.	11/1/38—A lesion at the opening of the esophagus obstructs it 75-80%.	Uppermost portion of esophagus	Left cord paralyzed	Transitional cell ca	11/2/38—Chronic inflammation changes are noted in both bases. Right greater than left. 12/22/38—Basal one-fourth right lower lobe shows coarse mottling apparently due to bronchopneumonia. Trachea deviated to the right.	Absent	Had gastrostomy performed but died of aspiration bronchopneumonia 12/23/38.

P D 10 4/22/39	M 53	Cough Dysphagia	5 4	1/24/39—Barium enters respiratory system through a perforation at the upper end of the sternum. Cause of perforation not indicated.	Esophago-tracheal fistula	3/16/39—Esophagoscopy done elsewhere. Mass found growing from esophagus into trachea.	Upper portion of esophagus	Right paralyzed	Squamous cell ca and trachea	Clinically, had aspiration bronchopneumonia	Absent	Gastrostomy done, but patient died Autopsy confirmed diagnosis—Aspiration bronchopneumonia. Died 5/1/39
B F 11 6/13/39	F 57	Dysphagia	4	6/16/39—Barium stopped 2.5 cm below sternoclavicular joint. Barium has funnel shape, the narrow end being displaced to the right and narrowed to about 1 cm width for 10.0 cm. Patient starts coughing immediately.	Roentgen-rays taken a little later reveal a small amount of barium in tracheo-bronchial tree	6/17/39—Cricopharyngeus is spastic and swollen 3 cm below the cricopharyngeus, a cauliflower growth springs from the left post esophageal wall, partially obstructing lumen	Upper esophagus 3 cm below cricopharyngeus	Right paralyzed	Biopsy reported inflammation. Repeat requested but not obtained	6/16/39—Small amount of barium in tracheo-bronchial tree. Intense calcification wall of tortu No other pulmonary or pleural affection on roentgen-ray. Physical exam shows a both lung fields with coarse, moist rales	Absent	Sent to chronic institution where she died 7/12/39
C V H 12 6/13/39	M 54	Cough Dysphagia	12 4	6/20/39—Right pyiform sinus and 1.5 0 cm of esophagus show completely disturbed mucosal pattern. Flow of barium little interfered with	A minimal amount of barium can be noted in main right bronchus and trachea	7/10/39—Autopsy revealed a lesion in the first 1.5 cm of esophagus penetrating into trachea and almost obstructing it	Uppermost 15 cm of esophagus	Left paralyzed Right paresis	Squamous cell ca	6/11/39—Numerous pea and cherry sized metastases 6/27/39—First sized area of pneumonic consolidation in right costophrenic angle	Absent	Died of aspiration bronchopneumonia 7/10/39
P S 13 11/16/39	M 76	Dysphagia Pain	8	11/20/39—There is a defect in the hypopharynx and upper esophagus. Great difficulty in swallowing and spilling over of barium into respiratory system	Barium spills over into tracheo-bronchial tree	11/30/39—Left cord fixed. Right moves poorly. Spasm prevented further examination	Upper esophagus near epiglottis	Left paralyzed Right paresis	Not obtained	11/21/39—Small areas of bronchopneumonia above right and left diaphragms	Present	Gastrostomy done. Developed popliteal artery thrombosis and aspiration bronchopneumonia. Died 12/15/39

served during the first examination in eight of the thirteen cases. A subsequent examination in case 6 likewise demonstrated it. Thus in nine of the thirteen cases (69.2 per cent) barium was seen to spill over into the tracheo-bronchial tree. In an additional two cases (9 and 10) barium entered the air passages via fistulae (15.4 per cent). In the remaining two cases (5 and 8), aspiration could not be demonstrated during the single fluoroscopic examination which was done. However, patient 5 later developed marked swallowing difficulty and the clinical opinion as to cause of death was aspiration bronchopneumonia. Case 8 likewise, probably died of aspiration bronchopneumonia. It is felt that if follow-up examinations were done, aspiration might have been seen in every case. With some variations in each patient, the exhibition of aspiration was quite similar. There would be several forceful efforts at swallowing during which the barium would descend to the obstruction and then fill the proximal dilated portion of the esophagus. With continued swallowing efforts a variable amount of coughing would follow and then barium could be noted spilling over into the tracheo-bronchial tree. A trickle of barium could then be seen in the air passages. This could also be visualized on the radiographic films. In two of the nine cases fluoroscopy indicated severe swallowing difficulty but it was not until the films were read that barium could be detected in the tracheo-bronchial system.

Esophagoscopy showed the pathological process to be at or near the cricopharyngeus in each instance. Biopsy, when obtained, did not invariably prove the lesion malignant. Cases 3 and 5 had lesions in the pyriform sinus which interfered with esophageal function. In every patient the mechanism of swallowing was compromised.

Extremely significant was the condition of the vocal cords. Their status was noted in 12 of the 13 cases. Eleven of these 12 patients (91.6 per cent) had either one or both cords involved. No paralysis was present in patient 5 whose lesion lay in the pyriform sinus with the esophagus only secondarily affected. Patient 1 whose cords were not examined at the time of his illness, has since been examined. The cords showed good function. Malignancy was never proved in this case.

The pulmonary findings were closely associated with the phenomena of aspiration. Roentgen-ray or physical examination indicated the presence of bronchopneumonia in every case but the first (92.3 per cent). Repeated interval examinations were necessary because the pneumonic process did not become intense until late in the illness, presumably following massive or repeated aspiration. Spilling over from the esophagus into the air passages accounted for the observed pathologic process in every case but two, where esophago-tracheal fistula due to the malignancy explained it. That a low grade pneumonic process could take place due to aspiration, without roentgen-ray or physical confirmation was seemingly demonstrated in case 1. Aspiration was noted on fluoroscopy and roentgen-ray, yet no mediastinal, pleural or pulmonary pathologic process could be detected on roentgen-ray or clinical

study. However, had not his lesion been quickly relieved he probably would have gone on to develop the more advanced clinical picture. The presence of clubbed fingers in this patient, with no other apparent cause for their appearance, likewise seems to speak for a low grade, possibly long standing, pulmonary process.

The presence of clubbed fingers in more than a third of the cases (38.5 per cent) is an additional finding of interest and significance. The patients presented none of the usual causes for clubbing and we were hard pressed to explain its presence until the phenomena of aspiration were noted. We could then rationalize it on the basis of a low grade, chronic, pulmonary infection caused by repeated small aspirations. In every case which showed clubbing, except case 5, we were able to demonstrate aspiration. Only one examination was done on this patient who later developed marked swallowing difficulty. It is felt that repeated examinations would possibly have revealed it. Another patient (6) showed no aspiration during one examination, but demonstrated it during a second study. Those cases which showed aspiration, but no clubbing, possibly ran too acute a course to allow of its development.

Twelve of the 13 patients died. They all died of aspiration bronchopneumonia. Patient 1 on whom a diagnosis of malignancy was never proved, is alive. He has no swallowing difficulty at present. His chest is clear, but he still has markedly clubbed fingers. Repeated examinations have revealed no other condition which might have been responsible for their formation.

ANALYSIS OF LESIONS WHICH INVOLVED THE LOWER TWO-THIRDS OF THE ESOPHAGUS (CHART 2)

Seventeen cases, or 56.7 per cent of the total, fell into this group. Three of the patients were females. The average age was 65 plus years. The most common symptom was difficulty in swallowing, although substernal distress, expectoration, cough, and choking were noted. The patients waited an average of five months before seeking medical aid.

Roentgen-ray examination showed the esophagus to be affected in every case. Fluoroscopic observations, however, differed greatly from those found in the first group. The consistent interference with swallowing was not observed. In the two patients (17 and 18) who did have great difficulty, aspiration was demonstrated. In patient 17 barium spilled over from the esophagus into the trachea, in 18 a fistula was found. Thus in this group we could demonstrate overflow aspiration in only one case (5.9 per cent) and fistula in only one (5.9 per cent). The other 15 patients (88.2 per cent) showed no barium in the air passages. Aspiration may have been present, but was undetected in patient 27 who had bronchiectasis and later consolidation of the right lung as well as clubbed fingers, patient 29 had an abscess in the right lower lobe which likewise may have been due to aspira-

CHART II

ANALYSIS OF LESIONS IN LOWER TWO-THIRDS OF ESOPHAGUS The Cases Are Unselected, Being Entered on Chart in Succession According to Date Admitted

Age	Sex	Duration in Months	Roentgen-Ray and Fluoroscopic Examination of Esophagus	Aspiration	Esophagoscopy	Location of Lesion	Vocal Cord Status	Biopsy of Lesion	Chest Examination	Clubbing of Fingers	Course and Comment
44	M	2	12/17/36—Between 7.5 cm. and 15 cm. above diaphragm there is concentric narrowing. No dilatation above. 2/19/37—Beginning dilatation of proximal portion	None	12/29/36—At about 28 cm. from the incisors is an easily dilated granulating area	28 cm. from incisor teeth	12/29/36 O K 4/9/37 Paresis right	Squamous cell ca	5/14/37—Roentgen-ray chest negative	Not noted	Gastrostomy performed 6/24/37 of urinary retention following trauma due to falling out of bed
47	M	1	5/21/37—No dilatation. No delay. Third quarter of esophagus is inhomogeneous in character	None	5/22/37—There is an extensive cauliflower lesion 30 cm. from the teeth	30 cm. from incisors	Examined but not recorded	Acanthosis	5/21/37—Healed calcific fbc focus at base of left lung field with a small pleural effusion	Not noted	Died 10/19/37 where
46	M	2	7/1/37—Esophagus narrowed to lead pencil width. Oral portion widened to double but fluid passed undisturbed	None	7/14/37—30 cm. below incisors a web constricts the esophagus. No attempt made to go beyond stricture	30 cm. below incisors	O K	Not taken	7/1/37—Roentgen-ray of chest negative 7/28/37—Bronchopneumonic affection of lower two-thirds of right lung and lower half of left (post-operative)	Not noted	Patient died 7/29/37 of post-operative bronchopneumonia nine days after gastrostomy
54	M	7 1/2	5/10/38—Swallowing with difficulty. Upper half of esophagus is slightly dilated. In the center the lumen is rather abruptly narrowed to lead pencil width	A rare drop of barium is spilled over into air passages	Done elsewhere. Revealed carcinoma with ulceration and infection	Middle third	Not examined	Squamous cell ca	3/10/38—Two small areas of consolidation seen above left diaphragm which are probably inflammatory, but possibly neoplastic	Not noted	Had gastrostomy 10/18/37. Didn't show up again. Last seen 3/10/38
44	M	6 5	3/17/38—Patient swallows with difficulty. At junction of middle and lower two-thirds barium comes to a stop and from here enters left main bronchus. Further coughing interrupts study	Esophagogram shows bronchial fistula	Patient's condition did not warrant manipulation. Died before this could be done	Middle third of esophagus	Not examined	Not taken	3/17/38—Coarse nodding and pleural thickening in upper half right lobe and right costophrenic angle, most pronounced near hilus	Present	Died 3/24/38 of aspiration bronchopneumonia

F A 19 5/3/38	M 57	Dysphagia	6	5/5/38—A structure is present at the arch of the aorta which narrows esophagus to lead pencil width. Hardly any delay in swallowing	None	4/7/38—A cauliflower growth completely obstructs lumen 12 cm below cricopharyngeus	12 cm below cricopharyngeus	O K	Squamous cell ca	5/23/38—Roentgen rays chest negative	Absent	Died 5/31/38 pneumonia
L Z 20 6/28/38	M 60	Dysphagia	3	6/30/38—Napkin ring cauliflower new growth causing concentric partial obstruction with slight dilatation above. Moderate delay to passage of barium. Begins four fingers below clavicle 9/9/38—Food passes without delay	None	7/21/38—A lobulated mass completely filled esophagus 31 cm from incisor teeth	31 cm from incisors	Examined but not recorded	Squamous cell ca	6/25/38—Right hilus nodes enlarged 7/11/38—No evidence of pulmonary or cardiac pathology to explain clubbed fingers 9/9/38—Moderate increase of pulmonary markings with right lung	Present	Received radiation therapy and improved. Discharged to clinic 9/20/38 and not seen since. Physical examination revealed malignancy and rales both here. Died 1/15/39 elsewhere of starvation
A Mc 21 8/8/38	M 75	Dysphagia	4	8/8/38—Irrregularity at the lower end of the esophagus with slight dilatation and retention	None	8/11/38—38 cm from the incisors the lumen is narrowed by an obstructing mass	38 cm	Examined but not recorded	Squamous cell ca	No demonstrable pathology	Not noted	Died 9/12/38 of hemorrhage
H N 22 9/12/38	M 65	Dysphagia	2	9/19/38—Terminal 5 cm of the esophagus is involved with slight dilatation and retention above	None	9/22/38—At 40 cm from incisors a cauliflower mass occludes lumen	40 cm	Examined but not recorded	No evidence of malignancy. No repeat obtained	No demonstrable pathology	Not noted	Died 9/18/38 Circulatory collapse due to inanition
L T 23 9/14/38	F 58	Dysphagia	10	9/9/38—Globular filling defects of cherry size in the distal half of esophagus	None	Done elsewhere. Neoplasm in esophagus just above cardiac orifice	Lowest third	No record Done elsewhere	Squamous cell ca	9/19/38—No evidence of metastases. Decrease of pulmonary markings over both bases	Absent	Gastrostomy approximately June 1938 Died at home 12/8/38
B F 24 9/28/38	M 70	Dysphagia	5	9/28/38—There is a narrowing just above the diaphragm with a dilatation to twice the normal width above this	Not seen with this examination	Done elsewhere. Showed malignant growth lower end of esophagus	Lower end	No record Done elsewhere	Squamous cell ca	Examination unsatisfactory	Beginning?	Infected gastrostomy wound. Lost ground and died 11/27/38
G L 25 10/15/38	M 75	Dysphagia	1	10/17/38—Starting in the center of esophagus and extending for 4" is an irregular filling defect	None	10/19/38—A mass was found halfway down esophagus	Middle third	Examined but not recorded	Squamous cell ca	10/17/38—Pleural adhesions right costophrenic angle	Not noted	Died at home 12/27/38

CHART II (Continued)

Age	Duration in Months	Recent Roentgen Examination of Esophagus	Aspiration	Laryngoscopy	Location of Lesion	Vocal Cord Status	Biopsy of Lesion	Chest Examination	Clubbing of Fingers	Course and Comment
6	12	10/27/38—At middle third is an obstruction through which food does not pass in 1 hour	None	12/15/38—At approximately 27 cm from incisors there is a proliferative, grayish growth which constricts lumen	27 cm from incisors	O K	Squamous cell ca	11/17/38—A spherical shadow noted just in front of new growth, apparently a mediastinal lymph node metastasis. No inflammatory pathology on roentgen-ray or physical	Absent	Refused gastrostomy. Died January 1939 of starvation and cerebral accident
7	9	11/29/38—Extensive lesion present in the entire lower half of esophagus with partial obstruction	None	Not done. Downhill course too rapid	Entire lower half	Not examined	Not taken	11/3/38—Lipiodol study indicated bronchiectasis. 12/14/38—Consolidation of the right lung	Present	Died 12/14/38 of bronchopneumonia. Bronchiectasis may in part account for clubbing
8	6	11/22/38—There is a large new growth occupying the lower half of the esophagus. Three minutes after swallowing, the esophagus is practically empty	None	11/29/38—Lower portion has a proliferative lesion involving the anterior wall	Lower half	No paralysis	Squamous cell ca	11/22/38—Fibrotic lesions in the subclavian region of left apex and left bronchus suggesting bronchiectases	Absent	Developed a severe psychosis following gastrostomy. Sank into coma and died 3/15/38
9	2	1/25/39—There is a lesion in the esophagus extending from 4" below the incisors to 10" below the incisors with slight narrowing and some retention	None	No consent obtained	Middle third	Not examined	Not obtained	4/25/39—The right lower lobe contained a fist sized consolidation of chronic pneumonic affection with a peach sized abscess	Not noted	Died at another institution 5/9/39
10	3	5/10/39—From 5" to 10" from the incisors there is an absence of mucosal pattern and filling defect of the esophagus. There is slight retention and distention	None	5/12/39—There is an extensive lesion beginning below the cricopharyngeus	Middle third	No paralysis	Squamous cell ca	5/10/39—Slight clouding of the lung apex possibly the	Absent	Died at another institution 6/29/39

tion The complaint of dysphagia, present in all patients, undoubtedly referred to the variable amount of obstruction and delay which was noted in every instance

Esophagoscopy was done at this institution, or elsewhere, in 14 cases Two patients were too ill and one refused examination The diagnosis of malignancy could not always be verified All the lesions lay distal to the uppermost third of the esophagus

The good function of the vocal cords in this group contrasted sharply with their dysfunction in lesions of the upper third However, some difficulty was encountered in the tabulation of results of these cord examinations This arose because when the cords functioned well, a record of their status was not always entered on the patient's chart Whenever done, but not recorded, this was indicated in the individual tabulations In only one instance (14) was any affection noted, and in this patient only a weakness was seen

Pulmonary complications were greatly reduced in this group Ten patients had either no demonstrable pulmonary lesions (14, 19, 21, 22) or lesions probably unrelated to the esophagus (15, 16, 23, 25, 28, and 30) The two patients with aspiration (17, 18) showed pulmonary pathologic findings related to it The first had two small areas of consolidation, probably inflammatory, and the second, as expected, died of bronchopneumonia due to massive aspiration Patients 20 and 26 showed glands in the mediastinum These were in the region of the site of the lesion in the esophagus and were either metastatic, inflammatory or both In any case, their presence could safely be attributed to the esophageal malignant growth Patient 27 had a severe cough and lipiodol study indicated the presence of bronchiectasis Patient 29 had a peach-sized abscess in the right lower lobe Unfortunately, he refused further examinations and the mechanism of its formation could not be probed further The lesions in both of these cases may have been due to undetected aspiration

Clubbed fingers were present in three cases (18, 20, 27) The esophago-bronchial fistula explained its occurrence in patient 18 Patient 20 showed enlargement of the hilar nodes and increased markings of the right lung field A mediastinitis, inflammatory or neoplastic, may well have been present to account for the clubbing Patient 27 was shown by lipiodol study to have bronchiectasis This is an accepted cause for clubbing which possibly had no relationship to the esophageal lesion, or it may have been due to undetected aspiration

All of the patients died Whereas aspiration bronchopneumonia was the cause of death in every instance in the first group, among these patients the cause varied One patient (14) died of trauma and urinary retention following a fall Two died postoperatively, one (16) from bronchopneumonia, another (19) following esophagectomy Patients 20 and 22 died of starvation and inanition Starvation undoubtedly played some part in all these cases Patient 21 died from hemorrhage, another (23) from a

severely infected gastrostomy wound Patient 26 suffered from a cerebral accident and 28 from a severe psychosis. Both went quickly downhill and died Five patients (15, 22, 25, 29, 30) died elsewhere without accurate diagnoses and one patient (17) could not be traced Patient 18 who had a fistula died of aspiration bronchopneumonia

DISCUSSION

The symptoms and complications of esophageal neoplasms are best classified according to the location of the process A syndrome which deserves further emphasis appears when the uppermost third of the esophagus is involved

Features common to all of these lesions are

- a* Location at or near the uppermost portion of the esophagus
- b* Paralysis or paresis of one or both vocal cords
- c* Dysphagia
- d* Aspiration of ingesta into the tracheo-bronchial tree
- e* Pulmonary complications due to aspiration
- f* Frequent occurrence of clubbed fingers

The normal act of swallowing is a delicately coordinated combination of acts After mastication the food is rolled into a bolus and propelled to the back of the mouth By a series of automatic movements the posterior nares and mouth cavity are shut off The larynx is pulled upward under cover of the root of the tongue and the vocal cords approximated to close off the air passages At the same time the epiglottis forms a floor over which the bolus travels to the back of the pharynx and downward by peristalsis through the esophagus

An obstructive and infiltrative lesion at the uppermost portion of the esophagus, which involves one or both recurrent laryngeal nerves, not only disrupts the normal act of swallowing at a vital point, but opens the passage to the tracheo-bronchial tree by fixing some of the structures and interfering with the approximation of the vocal cords Under such circumstances, aspiration would not only be likely but well nigh unavoidable

In general this appears to be the mechanism at work in the cases located in the uppermost third The lesion disrupts the peristalsis at the very opening of the esophagus, at the same time that the obstruction causes a damming back of the ingested material In addition, some of the important structures, such as the epiglottis, may be fixed by the lesion Simultaneously, the smooth coordination of the laryngeal elements is broken by involvement of the recurrent laryngeal nerve or nerves The action of the inferior pharyngeal constrictors is somewhat distorted, but more important, the vocal cords fail to approximate and close off the air passages The ingesta spills over the dammed esophagus into the larynx and aspiration is inevitable Pulmonary complications, varying with the amount and type of aspiration, are

certain Twelve patients with lesions in the upper esophagus all died of aspiration bronchopneumonia Prior to the development of this terminal complication, varying inflammatory processes were observed The presence of clubbed fingers in more than a third of these patients is similarly predicated on the aspiration

The incidence of pulmonary complications dropped perceptibly when the esophageal lesions lay distal to its uppermost third Aspiration as a cause, was proved in only one case It might have been undetected in some others Vocal cord function remained intact, as compared to almost universal dysfunction in the first group

This can readily be understood when one considers the anatomical relationship of the recurrent laryngeal nerves to the esophagus In the uppermost third both nerves lie proximal to it On the right, the nerve loses contact with the esophagus below the subclavian artery On the left it remains close to it down to the arch of the aorta The dysfunction of the vocal cords associated with lesions in the uppermost portion of the esophagus is therefore easily explained In lesions of the distal two-thirds, no cord dysfunction is noted because the recurrent laryngeals are no longer in proximity to the esophagus The findings are therefore consistent with the anatomical facts

With lesions in the distal two-thirds of the esophagus, the low incidence of pulmonary complications appears related to the infrequency with which early overflow aspiration is encountered The intact vocal cord function constitutes an additional protection The vocal cord status is not known in the one patient of the second group who had aspiration It is possible that the carcinoma infiltrated upward sufficiently to involve one of the nerves It is likely, however, that although a combination of factors, as seen in the first group, makes aspiration almost inescapable—all these factors are not essential It appears reasonable to expect it when the back damming is great, and the general condition of the patient is poor, even when the lesion is in the distal two-thirds of the esophagus This has been observed by other workers with stenosis of the distal end due to cardiospasm Although all protective reflexes may remain anatomically intact—a general state of inanition might so raise the threshold of response and result in such sluggishness of reflex activity as to cause gross dysfunction

The esophageal lesions in this study were mainly neoplastic It would appear, however, that neoplasia is not an absolute prerequisite for this syndrome Nor need the recurrent laryngeal nerves be involved Aspiration, with its attendant complications, might be expected with any obstructive and disruptive lesion at the upper end of the esophagus, or about its opening as with lesions in the hypopharynx or pyriform sinuses Lesions in the larynx must certainly give varying amounts of aspiration Neoplastic stenosis in the upper esophagus, however, makes for such a combination of anatomical and physiological pathology as to make aspiration almost inevitable

Clinically, the lungs appear tolerant to the dripping of foreign material. Large or repeated aspirations, however, must eventually produce manifest signs and symptoms. As a corollary to this, the finding of pulmonary pathologic conditions, vocal cord paralysis, or clubbed fingers in the absence of a known primary should point strongly to the esophagus or its neighboring structures as the offender. The picture of strangulation following attempts at swallowing, heretofore considered pathognomonic of esophago-tracheal or bronchial fistula, must be revised to include the described possibility. Fluoroscopic barium study of the swallowing function, in addition to the esophageal study itself, should be routine in the examination of all esophageal lesions. It would be wise to incorporate this examination in the study of any lesion which might interfere with swallowing.

SUMMARY AND CONCLUSIONS

1 The findings in 30 consecutive patients who presented themselves at the Brooklyn Cancer Institute with esophageal complaints are analyzed.

2 The symptoms and complications of esophageal neoplasms are best classified according to the location of the process.

3 A syndrome which deserves further emphasis appears when the uppermost portion of the esophagus is involved. The common features of these lesions are:

- a Location at or near the uppermost portion of the esophagus
- b Paralysis or paresis of one or both vocal cords
- c Dysphagia
- d Aspiration of ingesta into the tracheo-bronchial tree
- e Pulmonary complications resulting from aspiration
- f Frequent occurrence of clubbed fingers

Aspiration pneumonia was responsible for all the deaths in this group.

4 The incidence of pulmonary complications dropped sharply when the esophageal pathology lay in its lowermost two-thirds. Likewise, the recurrent laryngeal nerve involvement, almost universal in the first group, was absent here. Even in this group, however, there was sufficient dysfunction to cause a rare instance of aspiration.

5 Although the esophageal lesions in this study were mainly neoplastic, it would appear that neoplasia is not an absolute prerequisite for this syndrome. Any combination of factors which resulted in similar anatomic or physiologic dysfunction might be expected to lead to similar complications.

BIBLIOGRAPHY

- 1. MCCUE, JOHN. Carcinoma of the esophagus, in Osler's Modern Medicine, 1908, Lea and Febiger, Philadelphia, 2, 101.
- 2. JACOBSON, C., TUCKER, G., and CRYER, I. H. Malignant diseases of the esophagus, in Nelson's Loose-Leaf Medicine, Thomas Nelson and Sons, New York, May 1925, 2, p. 83.

- 3 JACKSON, C, TUCKER, G, and CHERI, L. H. Paralysis of the esophagus, in Nelson's Loose-Leaf Medicine, Thomas Nelson and Sons, New York, May 1925, v, p 85
- 4 JACKSON, C, and JACKSON, C. L. Pulmonary symptoms due to esophageal disease, Transactions Section on Laryngology, Otology, and Rhinology, Am Med Assoc, 1933, p 197
- 5 VINSON, P. P, and KIMMELSTEIN, P. Carcinoma of the esophagus with unusual clinical manifestations, Ann Otol, Rhinol and Laryngol, 1938, xlvii, 804
- 6 VINSON, P. P. The diagnosis and treatment of diseases of the esophagus, 1940, Chas C Thomas Springfield, Illinois, p 5
- 7 VINSON, P. P. See reference 6, p 35
- 8 MATHEWS, R. W, and SCHWABH, T. G. Primary esophageal carcinoma, with especial reference to a non-stenosing variety, Jr Am Med Assoc, 1935, cv, 1591
- 9 KEEFER, C. S. The pleural and pulmonary complications of carcinoma of the esophagus, ANN INT MED, 1934, viii, 72
- 10 RASTELLI, E. Carcinoma Esofageo Complicato Da Penetrazione Degli Ingesti Nelle Vie Respiratorie, Riforma med, 1936, lii, 1245
- 11 JOUSSEAU, ME. Les formes respiratoires du cancer de l'oesophage, Ann d'oto-laryngol, 1935, v, 1053
- 12 VINSON, P. P. Malignant diseases of the esophagus, study of 1000 cases, Northwest Med, 1933, xxxii, 320

THE DEVELOPMENT OF PLASMA PREPARATIONS FOR TRANSFUSIONS^{*}

By MAX M. STRUMIA, M.D., and JOHN J. MCGRAW, M.D.,
Philadelphia, Pennsylvania

EXPERIMENTALLY plasma or serum was used as far back as 1871 by Bowditch¹ and a year later by Luciani². A very extensive bibliography of the earlier experimental works on serum and plasma is contained in Amberson's review³. In 1918 Ward,⁴ a captain in the British army, made a terse appeal for the use of citrated plasma in the treatment of emergencies at the clearing stations, and briefly outlined the advantages over whole blood.

As far as we know his appeal was not answered, and probably the first extensive clinical use of serum and plasma was begun by one of us in 1927. By 1931 citrated blood plasma was used routinely at the Bryn Mawr Hospital, in place of whole blood, especially in the treatment of certain hemorrhagic diseases and of streptococcic and pneumococcic diseases with publication of one of the outstanding cases by Nicholson⁵. At that time plasma was used fresh, that is blood was collected, the cellular elements were separated by centrifugation, the plasma removed by suction, mixed with an equal part of saline or saline glucose solution, to dilute isoagglutinins, and administered within 24 hours. This method of preparation of plasma remains the ideal method for securing, with relatively simple technic and elementary aseptic precautions, a safe material containing all the properties of blood plasma. It is, however, not practical, because it deprives plasma of one of its essential advantages, namely that of being immediately available for use in emergencies.

The widespread, practical use of plasma, particularly in emergencies, is dependent upon a proper method of preservation. It is this phase that we want to discuss in this brief review. Full consideration of this important problem is justified by the ever increasing number of clinical indications for the use of plasma.

A proper method of preservation may be considered one which, in the simplest manner, assures a safe sterile plasma possessing as many of the original properties as possible, and therefore having the largest therapeutic field of application.

The first method of preservation was naturally the keeping of plasma in the refrigerator at a temperature of $+6$ to $+8^{\circ}\text{C}$ in the liquid state. We noted very soon that this method, while very simple, was accompanied by progressive flocculation of the most unstable proteins, with consequent necessity for filtration. Among the early workers using citrated plasma for transfusion must be remembered Palazzo and Tenconi⁶ and Kartaševskiy

^{*} Presented at the Proceedings of the American College of Physicians, April 24, 1941.

and Filatov⁷ The latter stated that the fibrin-like filaments forming in liquid plasma on standing would disappear on heating, a phenomenon which we have been unable to confirm Kartašhevskiy and Filatov used refrigerated plasma up to 11 months old particularly for the treatment of hemorrhagic diseases

At least one death has been reported due to the transfusion of citrated plasma preserved in the refrigerator in the liquid state, without previous filtration This case, attended by Dr J H Lewis, was brought to our attention by Dr Cooksey of Detroit The patient, a boy, had not previously received any other transfusion The plasma was given for the correction of hypoproteinemia and extensive edema in the course of a nephritis The patient received 90 to 100 cc of undiluted plasma, in 20 to 25 minutes Asphyxial death was sudden and occurred while the plasma was still being administered This plasma had been separated from citrated blood about 24 hours after collection of the blood, and it had been preserved in the liquid state for 40 to 50 hours The plasma was not filtered, and evidence points to the presence of precipitates in it before administration Microscopic examination of the lungs (figure 1) showed extensive embolism of the smaller branches of the pulmonary artery by a pinkish staining material, with a coarse reticular structure, closely resembling fibrin Sections from other organs showed no such changes, since the fibrin-like precipitates had not gone through the filter of the lungs

Another danger associated with the preservation of plasma in the liquid state is bacterial contamination A chance contamination of the blood at the time of collection or during the process of preparation affords the organisms a favorable medium of growth so long as blood or plasma is kept in the liquid state Addition of bacteriostatic substances is of relative value only, and should not be relied upon too much Merthiolate, which has been most commonly used, has no appreciable effect in whole blood The addition of sulphonamids proposed by Novak⁸ and others opens a more hopeful field

Administration of plasma in which even a minimal bacterial growth has occurred causes severe reactions Recently after the safe administration of over two thousand transfusions of plasma, mostly preserved in the liquid state, we had the experience of five such severe reactions, all from the same lot of contaminated plasma⁹ Although bacteria could not be obtained in culture, probably due to the action of the merthiolate, they could be demonstrated in the smears from sediment obtained by prolonged centrifugation of the plasma in question Danger of such chance contaminations may be reduced to a minimum only by the adoption of strictly aseptic precautions in the collection of the blood and by the employment of a closed system for the separation, pooling and distribution of the plasma¹⁰ Excessive growth of a chance contaminant of plasma, with production of toxic pyrogenic substances, is best prevented by adoption of a method of preservation of plasma other than in the liquid state, as will be pointed out later

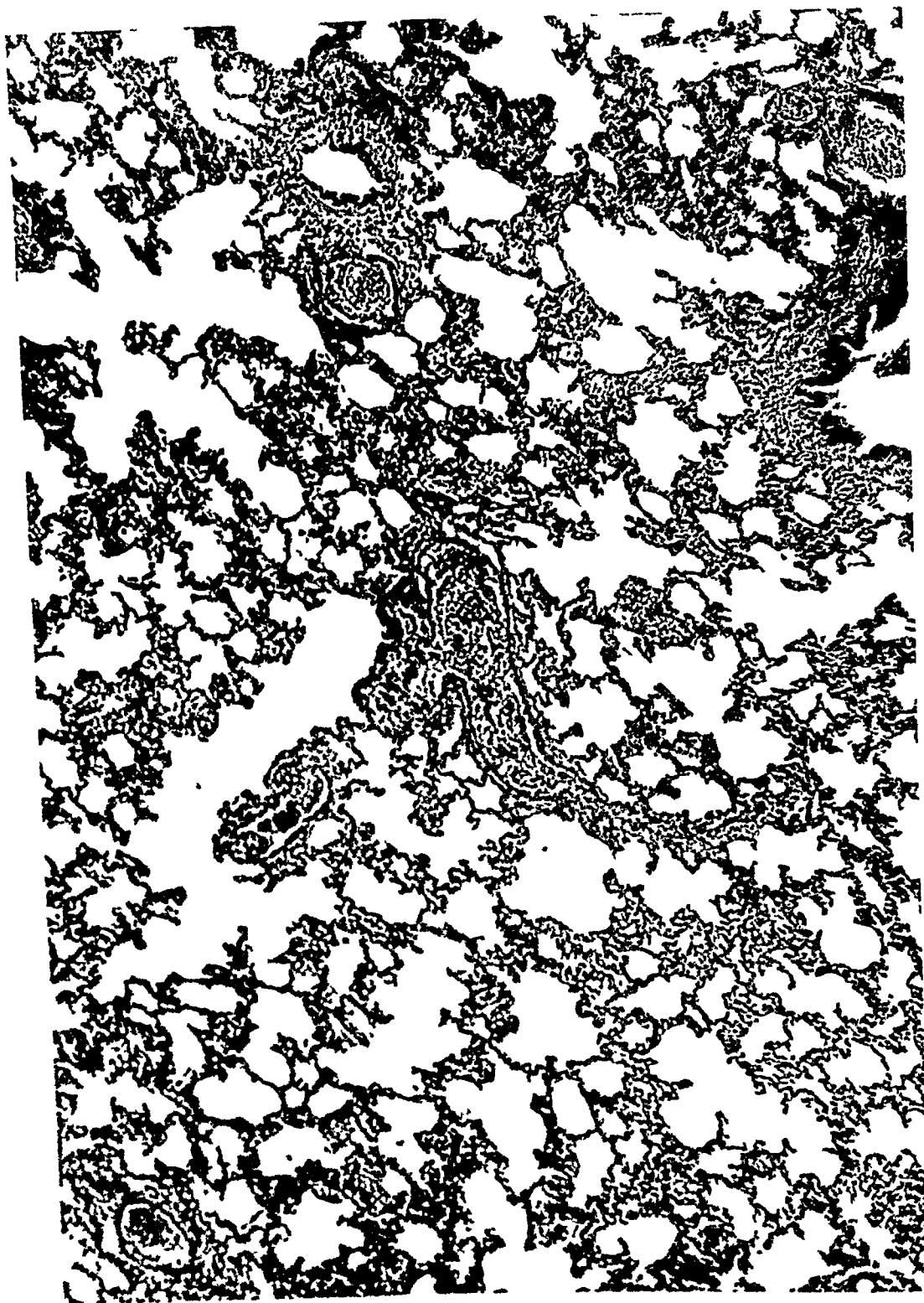


FIG. 1a. Multiple emboli of fibrin-like substance in branches of the pulmonary artery
X 64

A third objection to the storage of plasma in the liquid state is that there is a continuous and progressive loss of essential elements with aging, particularly of prothrombin and complement. This accompanies the flocculation already mentioned. Among the early advocates of the use of blood plasma is Ellor.¹⁴ He and his co-workers¹⁵ have recently recom-

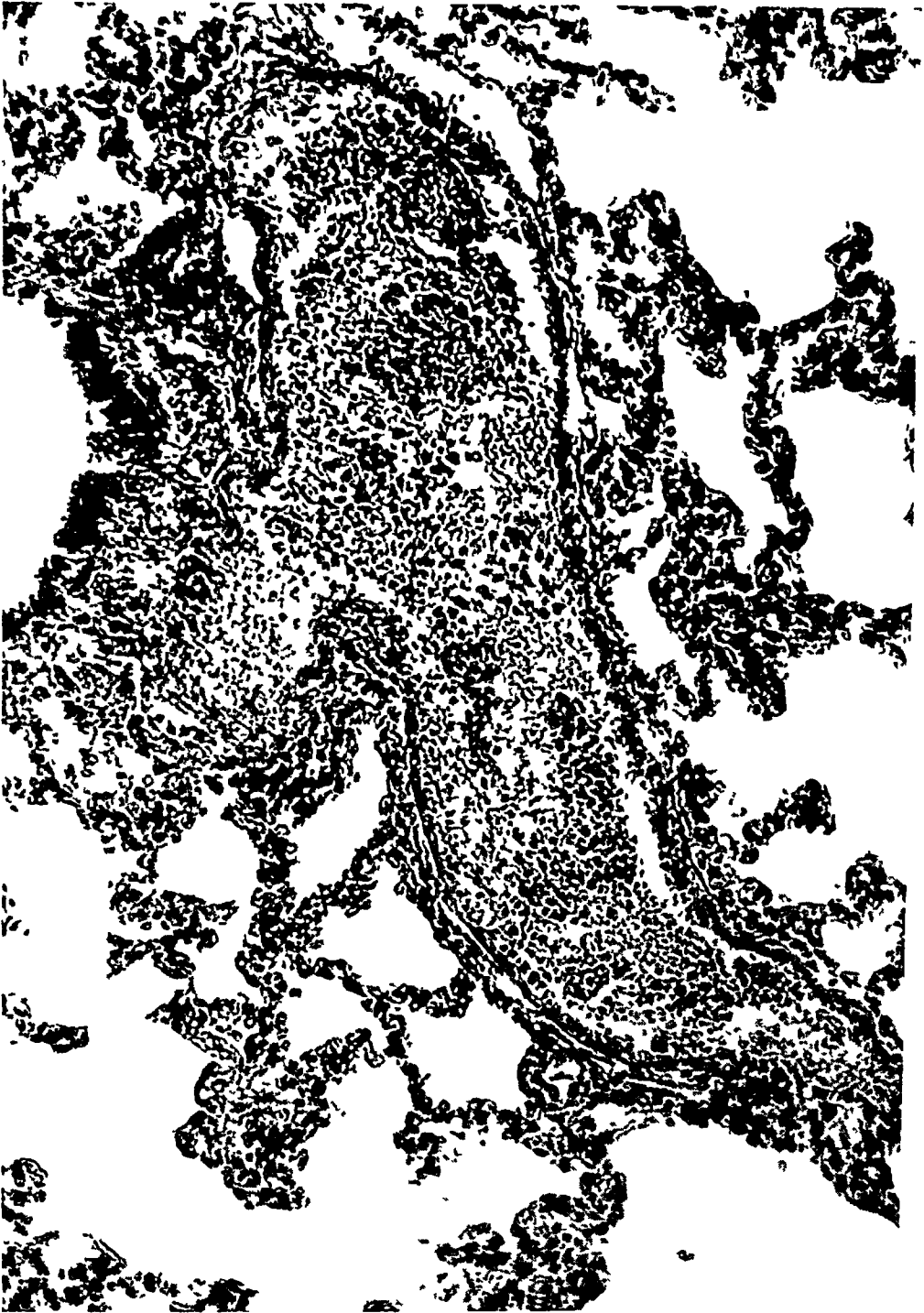


FIG 1 *b* Higher power magnification of embolus in a branch of the pulmonary artery
× 236

mended dilution of plasma with glucose solution to improve the preservation. The benefits from this procedure, however, are limited. For the reasons given above it is apparent that preservation of plasma in the liquid state at 4° C is to be discouraged.

The essential principles of drying of biological substances for the purpose of preservation laid down in the early part of the century by Vansteenberghe,¹³ Bordas and d'Arsonval,¹⁴ Shackell,¹⁵ Harris¹⁶ and Rogers¹⁷ were applied later on to the developments of methods suitable for the drying of serum by Elser,¹⁸ Reichel,¹⁹ Flosdorf and Mudd²⁰. Clinical applications of dried serum were made by Aldrich²¹ and Jeans²² for the treatment of nephrosis, by Hughes²³ for the relief of intracranial pressure, by Ravdin²⁴ for the treatment of hypoproteinemias, by Bond and Wright²⁵ for shock in experimental animals. Dried plasma was used by Mahoney²⁶ for treatment of experimental shock in laboratory animals, and Thompson²⁷ used the same material to prevent hypo-proteinemias and wound disruption in experimental animals.

Successful use of dried plasma in humans was begun in 1938 at the Bryn Mawr Hospital. The material was used especially for the treatment of shock and hypoproteinemias.²⁸

Since that time observations on the safety and efficacy of dried plasma or serum prepared by various methods have rapidly accumulated and numerous other methods of drying have been proposed, too numerous to mention. It would be entirely out of place to enter into the discussion of the relative merits or demerits of these methods. It will be sufficient to state that an acceptable method of drying of plasma must yield a product which is sterile, contains as many of the original properties of plasma as possible, is readily soluble, and has less than 1 per cent of residual moisture.

Recently in connection with work done under the auspices of the National Research Council, several hundred lots of plasma, each containing 17½ to 18 gm of plasma proteins were dried from the frozen state by a method employing the water vapor condensation by low temperature in vacuo. This material was distributed for experimental study to various institutions throughout the country, in receptacles allowing for regeneration with distilled water and direct administration. No reactions were reported in any of these tests except an occasional mild urticaria. The advantages of dried plasma are essentially the possibility of long storage and transportation under adverse conditions of climate, with opportunity for rapid restoration in emergencies. Furthermore dried plasma allows for restoration in concentrated form.

The drying of plasma, although a very interesting process and important under certain conditions, must not be allowed to overshadow the essentials of the general question of preservation as well as the practical consideration of clinical applications. The disadvantages of dried plasma are primarily the technical difficulties of its preparation, and consequently the high cost of the material as well as the inability to maintain any appreciable amount of prothrombin in the material thus prepared. It also appears that in the ordinary conditions of hospital procedure it is rather useless to remove water from plasma only to add it a few days later when a better method of preservation is available.

As far back as 1932 during an outbreak of poliomyelitis, it was found by one of us ^{28b} that plasma in the frozen state could be maintained for long periods of time without appreciable loss of any of its essential properties. However, on thawing flocculation occurred, which necessitated filtration before administration. Plasma thus prepared was used intravenously without reactions on numerous occasions. Thawing was done slowly, either at room temperature or at 4° C in the refrigerator. More recently, having reached the conclusion that drying of plasma could not for the reasons just mentioned solve the problem of preservation satisfactorily under all conditions, studies were resumed on the effect of temperature on the stability of plasma proteins. It was thus found that fresh plasma, just separated from citrated blood will remain clear for relatively long periods of time if kept at room temperature in the neighborhood of 25° C, but will rapidly flocculate if placed at 4° C. It was also found that if frozen plasma is thawed rapidly in the water bath at 37° C and allowed to warm to room temperature before being removed from the water bath, it could be kept at room temperature without visible flocculation for a relatively long period of time. However, if the plasma was removed from the water bath before it had a chance to warm at room temperature flocculation occurred, whether subsequently placed at 4° C or kept at room temperature. The initial freezing temperature and the temperature of preservation do not appear to be critical, so long as they are well below freezing in the order of —10 to —20° C. However, the time of thawing is critical, and it should be accomplished in 20 to 30 minutes at 37° C for optimal results.

Plasma frozen, maintained for several months in the frozen state and rapidly thawed in the manner described is practically indistinguishable from the original fresh material in the matter of turbidity (figure 2), content of all essential elements including the labile ones such as prothrombin, and therapeutic action. Plasma thus obtained has been successfully used at the Bryn Mawr Hospital routinely for several months. There have been no reactions.

It must be emphasized that regardless of the adequacy of the method of preservation, the final product can be no better than the plasma as originally separated from the blood. This emphasizes the necessity not only of the already mentioned aseptic precautions and the use of a closed method, but the shortening as much as possible of the time interval between collection of citrated blood and fixation of plasma by freezing. In this connection, separation of plasma by centrifugation must be mentioned as an essential step in the securing of an optimal product.

The advantages of preservation of plasma in the frozen state are the simplicity and economy of the method making it available to any hospital, the ease of storage and transportation, the optimal preservation of the more labile elements such as prothrombin and complement, the elimination of flocculation, and finally, the maintenance of sterility.

The employment of freezing and maintenance in the frozen state as a routine method of preservation of human plasma is not difficult because of the large variety of low temperature freezing cabinets now on the market for preservation of foodstuffs. Transportation of the frozen material for use away from the point of production or storage may be accomplished with the aid of CO₂ ice or in large quantities in refrigerated trucks. However,



FIG. 2 Effects of various means of preservation of citrated plasma

1	2	3	4
Preserved in the liquid state at 25° C for 21 days. Note moderate turbidity, but absence of visible precipitates.	Dried from the frozen state, regenerated with distilled water after 20 days and kept 24 hours at room temperature. Note considerable turbidity.	Frozen and kept in the frozen state for 20 days. Thawed rapidly at 37° C and kept 24 hours at 25° C. Note maximal clarity.	Preserved in the liquid state at 4° C for 21 days. Note flocculent precipitate.

All specimens are from the same lot of pooled citrated plasma (R C 57 A)

most cases requiring transportation will be practically handled by properly melting and warming of the frozen material at the place of storage. After this, it may be sent away for use to almost any distant point and will remain free of precipitate for several days so long as it is maintained at approximately 25° C. However, it is not advisable to keep plasma in the liquid state any longer than is necessary for the reasons outlined earlier. Thawed out plasma may be refrozen, if not used, without appreciable damage to its essential elements.

Thus plasma preserved in the frozen state possesses none of the disadvantages which led to the abandonment of storage in the liquid state, namely, ease of contamination, flocculation, and progressive loss of essential elements

In comparing dried and frozen plasma, the latter is seen to be superior in all but two respects. The dried material may be transported with greater ease under adverse conditions and it may be restored to a concentrated form if such be desired. It is estimated, that, in ordinary hospital routine and in emergency work, under the usual circumstances, over 90 per cent of the total need for plasma may be best met with material preserved in the frozen state

Every hospital may be easily provided with means of preserving plasma by freezing. Larger and better equipped hospitals may cooperate with many smaller institutions and easily dry plasma on a scale large enough to provide for the need of all. In this manner, with judicious use of frozen and dried material, the needs of everyone will be adequately met

The preservation of plasma in the frozen state opens the possibility for large scale storage of plasma for possible use in local or national emergencies. The material stored in standard containers may, when needed, be distributed either in the frozen state, or in the liquid state, after proper thawing, for immediate use. Finally, it may be dried from the frozen state, to meet needs as they arise

This method of combining preservation of the bulk of plasma in the frozen state, with possibility of drying at any time, does away with the expensive practice of drying of large stores of plasma

BIBLIOGRAPHY

- 1 and 2 Referred to by AMBERSON³
- 3 AMBERSON, W. R. Blood substitutes, *Biol Rev Cambridge, Philosophical Soc*, 1937, xii, 48
- 4 WARD, G. R. Transfusion of plasma, *Brit Med Jr*, 1918, i, 301
- 5 NICHOLSON, P. Notes on the treatment of an unusual case of hemolytic streptococcus septicemia, *Jr Pediat*, 1936, viii, 363
- 6 PALAZZO, R., and TENCONI, J. Plasmoterapia-Plasmiumunofusiones, *South Am Rev Endocrin, Immun and Enzyme Therap*, 1936, xviii
- 7 KARTASHEVSKIY, N. G., and FILATOV, A. N. Clinical study of transfusion of blood plasma, *Sovet. khir*, 1934, vii, 372
- 8 NOVAK, M. Use of bacteriostatic drugs in preservation of blood for transfusion, *Proc Soc Exper Biol and Med*, 1939, xli, 210
- 9 STRUMIA, M. M., and MCGRAW, J. J. Frozen and dried plasma for civil and military use, *Jr Am Med Assoc*, 1941, cxvi, 2378
- 10 STRUMIA, M. M., MCGRAW, J. J., and REICHEL, J. The preparation and preservation of human plasma
 - (a) Collection of blood and separation of plasma, *Am Jr Clin Path*, 1941, xi, 175
 - (b) Drawing off, pooling and distribution of plasma, *Am Jr Clin Path*, 1941, xi, 288
 - (c) Freezing of plasma and preservation in the frozen state, *Am Jr Clin Path*, 1941, xi, 388

- (d) Drying of plasma from the frozen state by low temperature condensation in vacuo, *Am Jr Clin Path*, 1941, xi
- 11 ELLIOT, J A preliminary report of a new method of blood transfusion, *South Med and Surg*, 1936, xcvi, 643
 - 12 ELLIOT, J, BUSBY, G F, and TATUM, W L Some factors and observations on preparation and preservation of dilute plasma, *Jr Am Med Assoc*, 1940, cxv, 1006
 - 13 VANSTEENBERGHE, P Procédé de conservation du virus rabique a l'état sec, *Compt rend Soc de biol*, 1903, iv, 1646
 - 14 BORDAS, F, and d'ARSONVAL Les basses températures et l'analyse chimique, *Compt rend Acad d sc*, 1906, cxlii, 1058, 1179
 - 15 SHACKELL, L F An improved method of desiccation with some applications to biological problems, *Am Jr Physiol*, 1909, xxiv, 325
 - 16 HARRIS, S E The properties of desiccated rabies virus and its use in antirabic immunization, *Jr Infect Dis*, 1912, x, 369
 - 17 ROGERS, L R P The preparation of dried cultures, *Jr Infect Dis*, 1914, xiv, 100
 - 18 ELSE, W J, THOMAS, R A, and STEFFEN, G I The desiccation of sera and other biological products (including microorganisms) in the frozen state with the preservation of the original qualities of products so treated, *Jr Immunol*, 1935, xxviii, 433
 - 19 REICHEL, J U S Patent Re 20969, 2066302
 - 20 (a) FLOSDORF, E W, and MUDD, S Procedure and apparatus for preservation in the "lyophile" form of serum and other biological substances, *Jr Immunol*, 1935, xxix
 (b) FLOSDORF, E W, and MUDD, S An improved procedure and apparatus for preservation of sera, microorganisms and other substances, the "cryochem-process," *Jr Immunol*, 1938, xxxiv
 (c) FLOSDORF, E W, STOKES, F J, and MUDD, S The "Desivac" process for drying from the frozen state, *Jr Am Med Assoc*, 1940, cxv, 1095
 - 21 AIDRICH, C A, and BOYLE, H H Concentrated human blood serum as a diuretic in nephrosis, *Jr Am Med Assoc*, 1940, cxiv, 1062
 - 22 JEANS, P C The use of lyophile serum, *Jr Iowa State Med Soc*, 1939, xxix, 64
 - 23 HUGHES, JOS, MUDD, S, and STRECHER, E A Reduction of intracranial pressure by concentrated human lyophile serum, *Arch Neurol and Psychiat*, 1938, xxxix, 1277
 - 24 RAVIN, I S, STENGLE, A, and PRUSHANKIN, M The control of hypoproteinemia in surgical patients, *Jr Am Med Assoc*, 1940, cxiv, 107
 - 25 BOND, D D, and WRIGHT, D G Treatment of hemorrhage and traumatic shock by the intravenous use of lyophile serum, *Ann Surg*, 1938, cxvii, 500
 - 26 MAHONY, E B A study of experimental and clinical shock with special reference to its treatment by the intravenous injection of preserved plasma, *Ann Surg*, 1938, cxviii, 178
 - 27 THOMPSON, W D, RAVIN, I S, RHOADS, J E, and FRANK, I The use of "lyophile" plasma in correction of hypoproteinemia and prevention of wound disruption, *Arch Surg*, 1938, xxxvi, 509
 - 28 (a) STRUMIA, M M, WAGNER, J A, and MONAGHAN, J F The use of citrated plasma in the treatment of secondary shock, *Jr Am Med Assoc*, 1940, cxiv, 1337
 (b) STRUMIA, M M, WAGNER, J A, and MONAGHAN, J F The intravenous use of serum and plasma fresh and preserved *Ann Surg*, 1940, cxii, 623

TOXIC DEPRESSION OF THE MYELOID ELEMENTS FOLLOWING THERAPY WITH THE SULFON- AMIDES; REPORT OF 8 CASES¹

By SOLOMON S RINKOFF, M D , and MAXWELL SPRING, M D ,
Bronx, New York

THE discovery of the therapeutic effectiveness of sulfanilamide and its related substances constitutes one of the greatest advances in medical therapeutics rivaling that of arsphenamine and its compounds in the treatment of lues, and that of quinine in the treatment of malaria.

The medical profession embraced these new drugs with great enthusiasm, and their use became widespread. Soon, however, reports of toxicity following the administration of these related substances appeared in the literature. Leukopenia, granulocytopenia and agranulocytosis were three of the more serious of the toxic manifestations.

Young¹ in 1937, and Johnston² in 1938 were the first to report cases of agranulocytosis following the administration of sulfanilamide and sulfapyridine respectively. Since then, there have been other reports of the occurrence of this complication. Filler,²² and Kennedy and Finland²³ in January 1941 reported the occurrence of agranulocytosis following the use of sulfamethylthiazole and sulfathiazole respectively. In this communication, we wish to record cases of leukopenia and agranulocytosis which have occurred in The Bronx Hospital following the use of neoprontosil, sulfanilamide and sulfapyridine.

CASE REPORTS

Case 1 Leukopenia following sulfanilamide therapy I R, a nine-year-old girl, was admitted to the Surgical Service of Dr J Cohen of the Bronx Hospital on February 7, 1939 for a painful swelling of the right forearm of one day's duration. Physical examination revealed an acutely ill child with a temperature of 104.2° F, pulse of 128, and respirations 28 per minute. On the lateral proximal portion of the right forearm there was an irregular, tender, erythematous, indurated area, two by three inches in diameter. There were lymphangitic streaks extending up the medial and lateral aspects of the arm. The right epitrochlear and axillary lymph nodes were enlarged. There were no other abnormal findings. A diagnosis of erysipelas, lymphangitis and lymphadenitis was made and wet dressings ordered applied locally. The next morning it was found that the lesion had spread, the temperature had risen to 104.6° F, and the pulse rate had increased to 132 per minute. Sulfanilamide was started at 9.30 a m, 20 gr (1.3 gm) being given at once and 10 gr (0.6 gm) ordered every six hours. The infection responded well to this therapy, and in 24 hours the temperature dropped to normal and the erythematous area began to fade and diminish in size. However, after the patient had received 65 gr (4.3 gm) of sulfanilamide (last dose at 10 a m on February 9), it was discovered that she was developing a leuko-

* Received for publication December 9, 1940
From The Bronx Hospital, New York

penia, and the drug was discontinued at once. In spite of its discontinuance, the number of white cells continued to decrease, and by the morning of February 11 was 3800 per cu mm (table 1). The patient was given pentnucleotide 10 c c twice a day and 5 c c liver extract twice a day. She also received 1200 c c of citrated blood on February 11 and 12 in divided doses of 200 c c each. Following these measures she improved rapidly and was discharged on February 15.

Comment. A leukopenia, which was recognized early, developed after 65 gr (4.3 gm) of sulfanilamide. The number of white blood cells continued to fall for two days after the drug was discontinued. A good response followed energetic therapy.

TABLE I

	Hemo- globin % Sahli	Red Blood Cells	White Blood Cells	Band Forms	Polymorpho- nuclears	Lympho- cytes	Mono- cytes
Feb 8	96	5,320,000	14,950	10	54	30	6
Feb 9	90		6,500	10	48	42	
Feb 10, 9 a m			5,200	6	44	46	
Feb 10, 6 p m			4,600	18	30	52	
Feb 11, 11 a m			3,800	3	27	64	4
Feb 11, 10 p m			14,000	28	40	32	
Feb 12	116	6,210,000	20,550	22	64	14	
Feb 13			20,200	18	76	6	
Feb 14	96	4,860,000	11,600	6	68	26	

Case 2. Agranulocytosis following sulfanilamide therapy. I. C., a 62-year-old white male, was admitted on December 23, 1938 to the Genito-Urinary Service of Dr. M. Loeb complaining of nocturia, frequency and dribbling of four years' duration. Cystoscopy revealed trabeculation of the bladder and an enlarged prostate. The patient left the hospital against advice on December 29, 1938. He stayed at home for an interval of about six weeks, during which time he became weak, lost his appetite, lost weight, and developed a swelling of his left testicle. He passed blood clots and calculi in his urine on February 8, 1939, and was readmitted to the hospital on February 10, 1939 with a temperature of 100.9° F., and pulse of 100 per minute. Physical examination revealed an elderly male subacutely ill. The skin showed evidence of loss of weight. The tonsils were hypertrophied and cryptic, the gums were infected and the submaxillary glands were enlarged. There were moist râles at both bases and in the left axilla. The heart had a regular sinus rhythm, there was a systolic blow over the apex and aortic area. Blood pressure was 126 mm. mercury systolic and 68 mm. diastolic. Abdomen was negative. Rectal examination revealed a moderately hard markedly hypertrophied prostate. The left epididymis was swollen and tender. Laboratory data: Urine-specific gravity ranged between 1.012 and 1.018, albumin between one and two plus, sugar negative, microscopic, numerous white blood cells and red cells. Blood: Hemoglobin 82 per cent Sahli, red blood cells 5,020,000, white blood cells 7200, polymorphonuclears 71 per cent, lymphocytes 15 per cent, monocytes 3 per cent, eosinophiles 1 per cent. Wassermann and Kahn tests negative. Blood electrolyte normal. Examination of the passed calculus showed it to consist of calcium oxalate and fibrin.

Electrocardiogram was negative on two occasions.

Cystoscopies on February 15 and February 23 revealed a marked hypertrophy of the prostate, trabeculation of the bladder. The bladder contained much blood and

encrusted pus. On March 4 a suprapubic cystotomy was performed. The next day the patient had an attack of pain in the right chest, accompanied by hemoptysis, cyanosis, and dyspnea. His temperature rose to 104° F, and the pulse to 120 per minute. A diagnosis of pulmonary infarction was made, and the patient was placed in an oxygen tent where he was kept for four days. On March 11 it was found that the suprapubic wound was infected, the culture showing gram positive cocci overgrown by *Bacillus proteus*. On March 14 the patient developed sticking pain in the left chest. The next day bronchial breathing was heard over the left lower lobe. A roentgen-ray of the lungs revealed irregular infiltration of both bases, interpreted as bronchopneumonia.

To combat the bladder infection, sulfanilamide was started on March 13, 1 gm every four hours. This was given until March 19. On March 24 sulfanilamide was resumed, 10 gr being given twice daily until April 8. The patient's temperature, which fluctuated between 100–103° F between March 13 and March 25, gradually subsided to 99.4° F by April 1. On April 6 the patient was given a blood transfusion of 500 cc. On April 7 his temperature rose suddenly to 103° F. A blood count taken on April 8 revealed a hemoglobin of 52 per cent Sahli, red blood cells 2,800,000, white blood cells 2150, with a differential of 3 per cent band forms, 82 per cent polymorphonuclears and 15 per cent lymphocytes. The sulfanilamide was discontinued at once. On this day the sulfanilamide blood level was 2.2 mg per cent. The next day, April 9, the patient's temperature rose to 104° F, he vomited and had liquid stools. Examination of the blood at this time revealed a white cell count of 3250, but no polymorphonuclears were found. Examination of the bone marrow (sternal puncture) revealed an aplastic type of agranulocytic marrow. (See table 2 for detailed description.)

TABLE II
Case 2

	Hemo- globin % Sahli	Red Blood Cells	White Blood Cells	Band Forms %	Poly- morpho- nuclears	Eosino- philes	Lympho- cytes	Mono- cytes	Plasma cells
Feb 12	82	5,020,000	7,200		71	1	25	3	
Mar 18	54	3,500,000	13,000	8	70		18	4	
Apr 8	52	2,800,000	2,150	3	82		15		
Apr 9	50		3,250	Only lymphocytes on smear					
Apr 10	82	4,080,000	700				99		1
Apr 11	82	3,980,000	450				99		1

Apr 11, bleeding time 2½ minutes—coagulation time 2½ minutes

On April 9 the nose and throat consultant found a beefy red tongue and dry mucous membranes. The tip of the tongue showed slight edema. The surface of the left tonsil had a slight grayish discoloration, apparently the beginning of a necrotic patch. The nasal mucosa was dry and slightly yellowish. His impression was agranulocytic angina in the pre-ulcerative stage.

The patient was given liver extract, pentnucleotide and two blood transfusions. But in spite of the fact that his hemoglobin rose to 82 per cent and red blood cells to 4,080,000, the white blood cells dropped to 450 per cu mm with no granulocytes. His temperature rose to 105.6° F, his respiration became rapid and very shallow, and he expired on April 11.

Necropsy findings were as follows (Courtesy of Dr Joseph Felsen)

Gross Pathology Multiple ulcers of skin about cystotomy wound

Hemorrhagic cystitis

Prostatic hypertrophy

Diverticulosis coli

Induration of the pancreas

Congestion of liver and spleen

Membranous gastritis

Congestion of lower lobes of both lungs with multiple infarction

Small atheromata of aorta and pulmonary artery

Histopathology

Lungs There was marked congestion of the pulmonary vessels with partial atelectasis and pulmonary edema. Another section showed vascular thrombosis with infarction of the adjacent pulmonary tissue.

Liver There was congestion of the liver sinusoids (chronic passive congestion). The sinusoids were markedly dilated in one section. There was an encapsulated area of focal calcific deposit present.

Kidney There was marked degenerative disease of both the parenchymatous and glomerular elements. The former showed marked cloudy swelling and glandular degeneration with separation of cells from the basement membrane. The latter were the seat of chronic fibrotic change. There were many areas of focal necrosis with round cell infiltration. A few focal areas of calcific changes were seen. A subcapsular papillary adenoma was present.

Bladder There was necrosis of the mucosa with diffuse round cell infiltration. There were focal areas of similar nature deeper in the wall, but no polymorphonuclear cells were seen. There was considerable edema of the sciosa, and numerous multinucleated giant cells were present.

Prostate Showed considerable fibrous change. Many of the glands were cystic and lined by atrophic epithelium. A large degeneration cyst was present.

Pancreas A fine diffuse fibrosis was present, with numerous focal areas of fat deposit.

Stomach Section taken through membranous area showed most intense necrosis of tissue with interspersed foci of clumped bacteria.

Vertebral bone marrow The marrow was quite fatty and showed an apparent deficiency in granulocyte production. Many megakaryocytes were present.

Smears from the spleen and liver disclosed large numbers of gram positive spore-bearing bacilli.

Sternal bone marrow examination on April 10 revealed the following: Leukocytes—2150 per cu mm. Nucleated red blood cells 900 per cu mm. No megakaryocytes were seen. Leukocyte—red blood cell ratio equals 23:1. Differential: promyelocytes 0.5 per cent, myeloblasts 3.5 per cent, lymphocytes 55 per cent, monocytes 2 per cent, reticular cells 1 per cent, Turk cells 3.5 per cent, plasma cells 4 per cent, erythroblasts 8 per cent, normoblasts 20 per cent, megaloblasts 2.5 per cent.

Interpretation—marked depression of all elements of bone marrow. Granulocytes are absent except for their earlier precursors, the marrow consisting chiefly of a few nucleated red cells and nonnuclear cells of various types: the hypoplastic or aplastic type of agranulocytic marrow.

Comment—A case of agranulocytosis following the administration of 15 gm sulfanilamide which ended fatally in spite of therapy. As in the previous case the white count continued to fall in spite of the discontinuance of the drug.

Case 3—Intravenous folic acid sulfanilamide therapy. M. N., a 39-year-old male, was admitted to the private clinic of Dr. Paul Cantarin of the Bronx Hospital with "stomach trouble" for 2 days, and sore throat of three to four days.

duration. He was given salicylates by his physician on the first day and then received 4 gm sulfanilamide on the third day. After he received the sulfanilamide he began to vomit profusely, and his general condition became worse. He became delirious and was referred to the hospital on July 14, 1939 at 3 30 p m. There was no history of the ingestion of drugs prior to this illness, except that he took aspirin for headaches. Upon admission physical examination revealed a delirious middle-aged white male with a temperature of 105.2° F, pulse rate of 110, blood pressure 120 mm Hg systolic and 85 mm diastolic, and respiration of 22.

The pharynx was markedly congested, and there were exudates over both tonsils and posterior pillars. The cervical glands were enlarged. Heart, lungs and abdomen were negative. About two hours after admission a punctiform erythematous rash appeared over the patient's body, particularly over the lower anterior chest and abdomen.

Laboratory Data. Urine specific gravity 1.018, albumin 2 plus, sugar and acetone negative. Microscopic examination revealed many cellular and granular casts. Blood sulfanilamide 47 mg per 100 c c. Blood culture negative. Blood Hemoglobin, 94 per cent (13.6 gm), red blood cells 4,700,000, and white blood cells 600. Differential: No polymorphonuclears, lymphocytes 90 per cent, monocytes 10 per cent.

A diagnosis of agranulocytosis was made and the patient was immediately given a transfusion of 500 c c of citrated blood and liver extract parenterally.

The next morning a blood examination revealed 900 white blood cells with 94 per cent lymphocytes and 6 per cent monocytes. Another blood transfusion of 350 c c was given, but the patient's condition remained the same and he expired suddenly that evening.

Postmortem examination (necropsy was performed by Dr. Louis Lefkowitz, Assistant Medical Examiner of Bronx County, about 17 hours after death).

There was diffuse erythema of the skin over the lower part of the chest anteriorly. There were no petechiae.

Gross. The brain was normal. There was no intracranial hemorrhage.

Chest. The pleural cavities were clear. The lungs were deeply congested particularly so posteriorly on both sides. No consolidation was evident. The bronchi and pulmonary vessels were normal.

Heart. The pericardium was normal and contained a normal amount of clear serous fluid. The left ventricle was moderately hypertrophied. The musculature was pale. A few yellowish plaques were present on the mitral cusps, otherwise the valves were normal. The coronary arteries were normal. The aorta showed a few atheromatous plaques in the abdominal portion.

Abdomen. The peritoneal cavity was clear.

Stomach. The mucosa was intensely hemorrhagic throughout, there were discrete hemorrhagic flecks and spots scattered on all walls. The intestines were normal.

Liver. The liver was normal except for the presence of deep congestion on section.

Kidneys. Both kidneys were larger than normal. The capsules stripped readily but left large depressed stellate scars which were apparently old. On section, the cortex was somewhat reduced and the markings were distinct. The pelves, ureters, and bladder were normal. The prostate was normal. The pancreas and adrenals normal.

Spleen. The spleen was four times the normal size. The malpighian bodies were not seen.

Testicles. The right was missing. The left was normal.

Sternum. The sternum on section showed a dark red marrow. Microscopically a section of the sternum revealed a well functioning bone marrow with active production of megakaryocytes, erythrocytes, and myelocytes in various stages of maturation. Unfortunately, permission for microscopic study of the other organs was not granted by the medical examiner.

Comment The marked vomiting, the rash, and the absence of any other predisposing drug all point to sulfanilamide as the cause of the agranulocytosis

Case 4 The next two cases of agranulocytosis, while not unequivocal, may be due to a combination of sulfanilamide and prontosil therapy.

A E., a 66-year-old white woman, developed a sore throat and fever on August 15, 1939. The next day a diagnosis of diphtheria was made by Dr. I. Greenberg, a physician of South Fallsburg, New York, and 5000 units of diphtheria antitoxin were administered. The diagnosis was confirmed by the New York State Department of Health Laboratories. The patient did not improve, and her temperature rose to 104° F. on August 18. Neoprontosil (20 c.c.) was given intramuscularly, sulfanilamide (gr. 5 every three hours) was started and eight doses were given. However, she did not improve, and developed definite ulcerations of the throat and palate by August 20. A smear taken from the ulcerations revealed Vincent's organisms. Gentian violet was then applied locally and 0.6 gm. neosalvarsan was given intravenously. The lesions in her mouth improved, but her general condition became worse. Her temperature rose to 105° F., and the respirations increased to 48 per minute. She was admitted to The Bronx Hospital on August 24, to the private medical service of Dr. S. Stein.

Physical examination upon admission revealed a very acutely ill, elderly female, somewhat cyanotic. The tongue was dry and crusted. The mucous membranes of the mouth were tinted with gentian violet. There was slight ulceration of the posterior palate. The heart was negative except for a sinus tachycardia. Examination of the lungs revealed impaired resonance and râles at both bases.

Laboratory data. Examination of the blood revealed a hemoglobin of 90 per cent Sahli, red blood cells 4,300,000, and white blood cells 1200. The differential revealed 2 per cent polymorphonuclears, 82 per cent lymphocytes, 2 per cent monocytes, 14 per cent plasma cells, and 2 per cent normoblasts. All the polymorphonuclears had toxic granules. Roentgen-ray of the chest was negative. Throat culture was negative for diphtheria.

The patient sank rapidly and expired a few hours after admission to the hospital.

Comment Very thorough questioning of the family, Dr. I. Greenberg, and Dr. S. Stein, her family physician, failed to elicit the history of the ingestion of drugs for two years prior to this illness. A single dose of atspheganine has been reported to have produced agranulocytosis,³ although the usual occurrence is an aplasia of all bone marrow elements, which did not take place in this instance. Sepsis, per se, may also cause depression of the myeloid elements. However, in view of the rather frequent occurrences of agranulocytosis following the use of sulfonamides as compared to the rare occurrence due to neoarsphenamine and sepsis, we feel that the sulfanilamide and the neoprontosil (totaling about 50 gr.) were at least partly instrumental in having caused the agranulocytosis.

Case 5. Agranulocytosis and toxic hepatitis following sulfanilamide. B. A. was admitted to The Bronx Hospital on February 25, 1939, to the private medical service of Dr. J. Link. She gave the following history: Five weeks prior to admission she developed a severe infection of the throat. She was attended by Dr. J. Link, who gave her 12 capsules of penicillin intramuscularly and 100 mg. of ascorbic acid daily. In a period of three days she improved. About February 15 she began to feel ill. She did not call her physician but took the remaining four capsules. She continued to feel ill until February 23, when she had

chills, sore throat, diffuse pains and aches, and temperature of 105° F. Examination at that time revealed a small exudate on the right tonsil. A culture for diphtheria was negative. A smear showed numerous cocci in chains. On February 24 she was given 1 gm of sulfanilamide at 1 p.m. and again at 5 p.m. At 9 p.m. she received 10 c.c. of 5 per cent neoprontosil intravenously. That night her temperature rose to 106.4° F., she was nauseated and vomited. The next morning she received 1 gm of sulfanilamide. However, because her general condition became worse she was sent to the hospital.

Physical examination on admission revealed an acutely ill and restless young female, with a temperature of 105.8° F., pulse of 120, and respiration of 26 per minute. The mucous membranes were cyanotic. The throat revealed grayish exudates over both tonsils that could easily be removed by swabbing. The cervical glands were enlarged. The rest of the examination was negative. A blood examination on February 25 revealed the following: Hemoglobin 77 per cent, red blood cells 4,300,000, white blood cells 370, with a differential of 3 per cent polymorphonuclears and 97 per cent lymphocytes. The patient was given a transfusion of 300 c.c. citrated blood. On February 26 the exudate of the throat was more pronounced, and there was an ulceration of the left tonsil. The sternal bone marrow examined on February 27 was typical of the hypoplastic type of agranulocytic marrow, showing chiefly lymphocytes together with a few plasma and reticular cells. The granulocytes were markedly decreased in numbers. These few had toxic granules. On the same day the patient received 500 c.c. of citrated blood, and was started on Ironyl (Pentnucleotide plus liver extract). On February 28 it was observed that the patient was jaundiced, but her throat and general condition were definitely improved. From February 28 to March 4 the patient received four additional blood transfusions. She continued to improve slowly, and the number of white blood cells rose day by day, so that they numbered 8000 on March 13, a day prior to her discharge from the hospital (for blood studies see table 3).

TABLE III
Case 5

	Hemo- globin % Sahli	Red Blood Cells	White Blood Cells	Band Forms %	Poly- morpho- nuclears	Lympho- cytes	Mono- cytes	Transfusion
Feb 25	77	4,300,000	370		3	97		300 c c
Feb 27			830	40	10	46	3	500 c c
Feb 28			1,050	31	15	51	3	300 c c
April 1			1,700	14	23	52	10	300 c c
2	76	4,500,000	1,650	6	16	74	3	300 c c
3			1,350	11	13	66	6	300 c c
4			2,300	8	10	74	8	
6			3,600	8	30	60	2	
7			4,900	11	38	50	1	
8			5,100	6	44	47	3	
9			6,350	8	55	32	5	
11			5,300	7	48	37	8	
13			8,000	2	67	29	2	

February 27, Sternal puncture. Leukocytes—5700 per cu mm. Nucleated red cells—800 per cu mm. Megakaryocytes—none seen. Nucleated white blood cells red blood cell ratio was 7:1. Differential: polymorphonuclears 2 per cent, band forms 8 per cent, young forms 1 per cent, myeloblasts 1 per cent, lymphocytes 71 per cent, monocytes 1 per cent, reticular cells 1 per cent, plasma cells 2 per cent, normoblasts 5 per cent, erythroblasts 6 per cent, megaloblasts 1 per cent.

Comment The patient took 40 grains of antipyrine salicylate five weeks prior to admission and 20 grains about 10 days prior to admission. She received a total of 3.5 gm sulfanilamide and neoprontosil. Whether antipyrine can produce agranulocytosis is still a debatable point. If it does, it must be a very rare occurrence, as there are only two cases on record (Groen and Gelderman⁴) of this complication.

Case 6 Leukopema due to a combination of sulfapyridine plus neoprontosil therapy F A, a 41-year-old white female, was admitted to the private surgical service of Dr. H. J. Epstein on July 5, 1939, because of frequency and incontinence of urine of one and one-half years' duration. Five years previously she had been treated for a kidney infection. Physical examination was normal except for the presence of a cystocele. The blood pressure was 120 mm Hg systolic and 80 mm diastolic. The laboratory findings were as follows: Urine—specific gravity 1.018, albumin trace, microscopic—numerous white blood cells, occasionally in clumps. Blood—hemoglobin 78 per cent (11.3 gm), red blood cells 4,400,000, white blood cells 9,800 with 74 per cent polymorphonuclear leukocytes, 3 per cent band forms, 15 per cent lymphocytes, 5 per cent monocytes, 2 per cent basophiles, and 1 per cent eosinophiles.

On July 6, under spinal anesthesia, the patient had a repair of the cystocele.

The temperature was normal until the second postoperative day when it rose to 104° F associated with a chill. She was thought to have pneumonia and was started on sulfapyridine. The temperature fell the next day to 100.4° F, and the sulfapyridine was stopped. (A roentgenogram of the chest on July 10 was normal except for an elevated right diaphragm.) However, the temperature started to rise again and on the fifth postoperative day, July 11, reached 105° F and 106° F. The temperature was associated with frequent chills, frequency and incontinence of urine. The urine, at this time, revealed one plus albumin, numerous white blood cells with occasional clumps and one or two red blood cells per high power field. *Bacillus coli* was found on culture. A diagnosis of pyelitis was made and the sulfapyridine was resumed. Thereafter the temperature was septic in type, varying from 99–106° F, with frequent chills. Repeated blood cultures were sterile. On July 13 the blood sulfapyridine concentration was 5.9 mg per cent. After having received 20 gm in a period of seven days, the sulfapyridine was discontinued on July 15 because it was ineffectual. Neoprontosil was started on July 20 but was discontinued on July 22 for the same reason, after a total of 6 grams had been given.

TABLE IV

Case 6

	Hemo- globin g Sahli	Red Blood Cells	White Blood Cells	Poly- mor- phonu- clears	Band Forms	Lymph- ocytes	Mono- cytes	Eosino- philes	Baso- philes	Plasma	Sulf- pyridine concentration
July 5 Admission	78	4,400,000	9,800	74	3	15	5	1	2		
July 8	84		24,350	96		4					
July 11	68	3,650,000	13,400	76	10	14					
July 12	62		13,900	70	18	4	6	1		1	
July 13	70		14,500	78	11	9	2				5.9 mg
July 14	70		12,000	72	16	5	7				
July 17	76	3,900,000	11,800	76	9	12	3				
July 19	68	3,700,000	9,200	53	26	16	5				
July 21	62		9,200								
July 22	58		7,600	50	20	24	4	1	1		
July 24	54	3,000,000	4,900	44	27	23	4			2	
July 25	70	3,700,000	3,300	58	22	16	4				
July 25			3,100	28	28	36	8				
July 26	74	3,800,000	2,900	40	22	28	10				0 mg
July 26			2,050	56	27	11	5	1			
July 27			2,500	26	32	21	8	2	1		
July 28	88	4,600,000	2,900	42	43	10	2	2	1		

Martin Loeb A culture from the abscess was sterile after 72 hours' incubation. Histologically, a section of the renal cortex showed acute and chronic pyelonephritis. Following the operation the nitrogenous elements of the blood fell to normal. Non-protein nitrogen 25 mg per cent, uric acid 3.1 mg per cent, creatinine 1.4 mg per cent. The patient's condition, however, became steadily worse, and she expired at 6:05 a.m. July 29, 1939. (See table 5 for blood chemistry studies.)

TABLE V

Case 6

	Blood Chemistry	Glucose	Non-Protein Nitrogen	Urea N	Uric Acid	Creatinine	CO ₂ Com- bining Power
July 15			115.4				52.2
		97.1	146.4	85.7	7.2	4.16	
July 16			105.3				
July 17		95.3	67.4	37.5	4.6	1.49	
July 18		104.7	47.6	25.6	5.2	1.17	
July 20			48.4				
July 23			50.2				
			50				
July 24		173.9	41.4	12.7	4.1	1.39	
July 25		87	25.9	12.9	3.1	1.40	

The urinalyses throughout the course showed a specific gravity varying from 1.005 to 1.013, 2-3 plus albumin, a moderate to a marked number of white blood cells with a moderate to a marked clumping tendency, and from an occasional to many red blood cells. Cultures revealed *Bacillus coli* and *Staphylococcus albus*.

Necropsy (Courtesy of Dr. Joseph Felsen)

Gross findings: Pulmonary edema and congestion. Red hepatization of the left lower lobe. Chronic passive congestion of the liver. Multiple cortical thromboses of

the left kidney with several small abscesses. Right pyohydronephrosis with gangrenous pyelitis, ureteritis and cystitis. Multiple hemorrhagic ulcerations of the ascending colon.

Microscopic findings There were focal areas of necrosis in the lungs, spleen, liver, pancreas and kidney which contained giant cells in their centers. These lesions were strongly suggestive of tuberculosis. The bone marrow section revealed some areas of focal necrosis, but other areas revealed active cell production and maturation and many megakaryocytes.

Comment The total number of white blood cells began to fall a day before the sulfapyridine was discontinued, i.e., after a total of 19 grams had been given, and then reached a level for a few days. Following the discontinuance of the neoprontosil therapy, they decreased a little more rapidly and were at their lowest level four days after the latter drug was stopped. The total dosage of both drugs was 26 grams over a period of 14 days, with a lapse of five days following the discontinuance of the sulfapyridine before the neoprontosil was given. Repeated transfusions, liver and bone marrow extracts brought about a slight increase in the number of white blood cells. However, the patient died before any real effect of this therapy could be noted, though histologically the bone marrow showed active cell production and maturation.

Case 7 *Agranulocytosis following sulfapyridine therapy* M. K., a 45-year-old white male painter, was admitted to the medical service of Dr. Henry Schumer on January 4, 1940 because of fever 99–102° F daily, anorexia, loss of weight and profuse sweats for six weeks. He had been in the hospital from October 23, 1939 to November 18, 1939 for a chronic sacroiliac strain. During that time he ran a low grade temperature, the cause of which was not determined. Blood culture was negative. His past history revealed the knowledge of the presence of a heart murmur for 22 years. There was no rheumatic history.

four hours. The temperature, which had ranged from 101 to 103° F, immediately fell to 99° F within 24 hours and continued about 100° F until January 15. Then it began to fluctuate between 100–103° F until January 20 when it again fell to 100–101° F. It continued at this level until January 25 when the sulfapyridine was discontinued because of the development of agranulocytosis. It rose terminally to 104° F. The total dose given was 89 grams. The blood sulfapyridine level during therapy ranged between 2.9 mg per cent and 8.9 mg per cent. The sulfapyridine was continued in spite of a poor response to its use as a preliminary to heparin therapy which was not instituted because of the development of an agranulocytic state.

During the first week the pulse was about 100, thereafter it ranged about 120 per minute, and gallop rhythm was present at the apex. The respirations were normal the first week, 20–22, slightly increased the second, 22–28, and moderately so thereafter, 24–36.

The patient went steadily downhill. Blood cultures remained positive. Blood studies showed a secondary anemia of moderate degree and a leukocytosis with polynucleosis. Moist râles were heard at the bases of the lungs from January 5 on. A roentgenogram of the chest on January 9 showed increased markings at the bases, more marked on the right side, and a slightly enlarged left ventricle. On January 23 sacral and ankle edema were first noted, and the liver, which had been about two fingers'-breadth below the costal margin, was now four fingers'-breadth below. The spleen was still not palpable. On this day, too, fundal hemorrhages and red blood cells in the urine were found for the first time as evidence of embolization. At 5 p.m. on January 23 the patient had a sudden attack of severe painless dyspnea and cyanosis. At this time the respirations were 36 per minute, the pulse 136 and the blood pressure 136 mm Hg systolic and 66 mm diastolic. There were diminished breath sounds and moist râles over the bases of both lungs. He was thought to have a pulmonary infarction. He was placed in an oxygen tent and was digitalized because of his congestive failure. An electrocardiogram on January 24 showed findings suggestive of a coronary occlusion. The icteric index on January 25 was elevated to 12.5. Another electrocardiogram on January 26 suggested the presence of a previous coronary occlusion and myocardial fibrosis. The patient who up to and including January 23 had a leukocytosis and a polynucleosis was found on January 25 to have a granulocytopenia with a leukocyte count of 776, polymorphonuclears 11 per cent, lymphocytes 69 per cent, monocytes 21 per cent. The sulfapyridine therapy was stopped. At this time the blood sulfapyridine level was 5 mg per cent. The sternal marrow findings revealed an almost complete absence of the granulocytic elements. That afternoon a citrate transfusion of 500 c.c. of blood was given and pentnucleotide 10 c.c. intramuscularly four times a day was started. By the afternoon of January 26 the white count had risen to 1344 but the polymorphonuclear leukocytes had fallen to 2 per cent with a rise in the lymphocytes to 98 per cent. Thrombopenia and abnormal clotting time were associated. No mouth lesions were present. The dyspnea continued, the edema increased, and the abdomen became distended. The patient did not respond to prostigmin. He expired at 3 a.m. on January 27, 1940, 23 days after admission. A sternal marrow examination performed 15 minutes after death was essentially similar to the previous one except that no granulocytic elements were present. (See table 6 for blood studies.)

Postmortem examination (Necropsy was performed seven hours after death by Drs. Kastl and Rothstein)

There was edema of the dependent parts and slight scleral jaundice. Petechiae were present in the right lower lid and over the chest and abdomen. No lesions of the mucous membranes of the mouth or pharynx were present.

Lungs. A moderate amount of pulmonary edema and congestion of the bases was present. Microscopic examination showed a large amount of pulmonary congestion.

TABLE VI
Case 7, M. K.

Cells	Neutrophils	Band forms	Lymphocytes	Monocytes	Eosinophils	Nucleated Erythrocytes	Basophils	Platelets	Clot Retraction	Bleeding Time	Coagulation Time	Red Cell Fragility	Icteric Index	Blood Sulfanilamide %	Blood Cultures per c c	Hippuric Acid Synthesis	Congo Red %
	83	1	10	6											240	3.36 g excreted	50%
	91	3	5	1										50	260		
														33			
														29	300		
														71			
														80			
														89	500		
1	5		79	0	16	16		30,000			3		12.5		Transfusion 500 c c 4.30 p m		
1	11		67	21		19		50,000									
1	14		72	0	14	8											
0	1		71		28	15		70,000	none after 24 hours	1½	4½	0.38	14.1		Smear of red blood cells, anisocytosis, poikilocytosis, macrocytes, microcytes, polychromatophiles		
6	2		98			18		40,000				to 0.30					

The alveoli were the seat of exudative and cellular changes. The intra-alveolar cells were largely mononuclear. Some atelectasis was present.

Heart. The heart was enlarged, weighing 700 grams. The pericardial sac contained 15 cc of serous fluid. Both ventricles were hypertrophied, the left being dilated. Examination of the valves showed numerous grayish-red vegetations on the mitral, aortic and the tricuspid valves. The mitral valve exhibited extensive ulceration of the leaflets. Several vegetations were seen on the left auricular endocardium, smears of which showed gram positive cocci in chains. The papillary muscles and chordae tendineae appeared hypertrophied. The coronary arteries showed slight atherosclerosis especially at their origin. On microscopic examination, the valves showed fibrinoid changes with necrosis and bacterial clumping. The underlying tissue of the valve was extremely cellular and contained many small and large mononuclear cells. Occasional giant cells and some fibroblasts were present. Considerable hyaline, myxomatous and fibrinoid degeneration was present. The endocardium exhibited similar changes with cellular infiltration of the underlying myocardium. The myocardium was normal except for a few small areas of round cell infiltration.

About 100 cc of yellow ascitic fluid were found in the peritoneal cavity.

Liver. The liver weighed 2350 grams and had a nutmeg appearance on section. Microscopically, there was marked chronic passive congestion with bile stasis.

Spleen. The spleen weighed 350 grams. On section it was dark and congested and showed 4 or 5 old and recent yellowish, white and red infarcts, the largest being 2 cm in diameter. Microscopic examination showed a large area of massive infarction, with perisplenitis. The sinusoids outside this area were markedly dilated.

Kidneys. The right weighed 300 grams, the left 250 grams. The capsules stripped easily. There were numerous old scarred areas on their surfaces which appeared to be old cortical infarcts. Microscopically, many of the glomeruli were found to be completely obliterated. A few of the glomerular tufts exhibited focal necrosis with suggestive embolization by bacteria. In some areas there was marked thickening of the capsule with partial or complete atrophy of the tuft. One large vessel showed what appeared to be recanalization.

The stomach, pancreas, gall-bladder, testicles, prostate, epididymis, and adrenals were normal. Microscopically, the adrenal exhibited a cortical adenoma.

Intestines. The jejunum, ileum and colon showed numerous small areas of punctate hemorrhages many of which were hard and felt like shots. Microscopically, several sections through the intestinal wall revealed thrombi in the submucosal vessels which probably represented non-bacterial embolization.

A left incarcerated inguinal hernia which contained a portion of sigmoid colon was present.

Bone. The vertebral bone marrow was dark red in color and microscopically revealed normal cellularity and constituents.

1/25 11 a m Sternal Marrow Puncture

Leukocytes 10000 per mm Ratio 1 47

Nucleated erythrocytes 47000 per mm

Megakaryocytes 20 per mm

Differential—Polymorphonuclear leukocytes	0.5%
Myeloblasts	0.5%
Lymphocytes	16.0%
Monocytes	0.5%
Normoblasts	44.0%
Erythroblasts	33.5%
Megaloblasts	5.0%

Almost complete absence of granulocytic elements

Numerous disintegrated cells are seen. The bone marrow thus exhibits a picture of agranulocytosis.

1/27 15 minutes after death 3 15 a m

Leukocytes	2200 per mm
Nucleated erythrocytes	20000 per mm
Ratio	1 10
Differential—Polymorphonuclear leukocytes	0%
Myeloblasts	1%
Lymphocytes	49 0%
Monocytes	1 5%
Normoblasts	40 5%
Erythroblasts	7 0%
Megaloblasts	0 5%
Megakaryocytes	0 5%

Essentially similar to previous Sternal marrow examination showing agranulocytosis

Comment The patient had subacute bacterial endocarditis and was given sulfapyridine as a preliminary to heparin therapy In spite of this, the blood cultures remained positive After a total of 89 grams of the drug had been given over a period of 17 days, granulocytopenia developed which went on to a complete agranulocytosis The blood sulfapyridine was 5 mg per cent when the granulocytopenia was found This condition did not respond to transfusion and pentnucleotide as evidenced by the postmortem sternal marrow examination It is difficult to say that the agranulocytic state was directly responsible for the patient's death, in view of his congestive heart failure Postmortem examination disclosed subacute bacterial endocarditis, congestive heart failure, and a vertebral bone marrow which exhibited normal cellularity and constituents The latter finding is not inconsistent with the agranulocytosis since the toxic process may selectively affect portions of the bone marrow. Thus, the section was probably made through a portion of marrow that either was not affected by the drug or had already regenerated

Case 8 Leukopenia following sulfapyridine therapy F A, a 57-year-old white female, was admitted to the private surgical service of Dr Martin Loeb on March 20, 1940 because of right upper quadrant pain of three days' duration Physical examination was essentially negative except for slight rigidity on the right side of the abdomen and bilateral costovertebral tenderness A roentgenogram of the gall-bladder showed failure of the organ to be visualized with the dye

Laboratory examinations. The urine contained a trace of albumin and 8-10 white blood cells per high power field The hemoglobin was 94 per cent (Sahli), the red blood cells 4,720,000 and the white blood cells 5,500 with 50 per cent polymorphonuclear leukocytes, 2 per cent band forms, 42 per cent lymphocytes and 6 per cent monocytes

cent lymphocytes, and 2 per cent monocytes. Prior to the institution of sulfapyridine therapy at 3 30 p m on April 6, the hemoglobin was 69 per cent, and the white blood cells 4,300. Two grams of the drug were given as an initial dose and then one gram every four hours. By 7 a m April 7, 17 hours following the institution of the sulfapyridine therapy, the patient had had 6 grams of the drug. At 10 a m the drug was discontinued when a blood count revealed a fall in the hemoglobin to 60 per cent and in the white cells to 1700, with 4 per cent polymorphonuclear leukocytes, 32 per cent band forms, 30 per cent young forms, 30 per cent lymphocytes, and 14 per cent monocytes.

In the afternoon of the same day, the white count was 1425 with 2 per cent polymorphonuclear leukocytes, 40 per cent band forms, 20 per cent young forms, 22 per cent lymphocytes, and 10 per cent monocytes. A transfusion of 400 c c of whole blood was given immediately, and pentnucleotide (10 c c intramuscularly) was started and continued three times daily until April 13, by which time the patient had received a total of 170 c c. The urine on April 8 revealed a faint trace of albumin and a negative benzidine reaction. Following the transfusion the patient improved rapidly. The hemoglobin and white cells rose, the latter on April 10 to 6,600 with polymorphonuclear leukocytes 62 per cent, band forms 10 per cent, lymphocytes 27 per cent, and monocytes 1 per cent, and then fell on April 12 to 5,400 with marked toxic granulation of the neutrophils. (See table 7 for blood studies.) By April 13 the lungs were normal. The patient was discharged on April 24.

TABLE VII

Date	Hemo- globin % Sahl	Red Blood Cells	White Blood Cells	Poly- mor- phonu- clears	Band Forms	Young	Lymph- ocytes	Mono- cytes	Eosino- philes	Plasma Cells	Turck Cells
3/20	94	4,700,000	5,500	50	2		42	6			
4/5	79	4,100,000	5,500	32	49		17	2			
4/6	(11 5 gm) 69 (10 1 gm)		4,300								
3 30 p m				Sulfapyridine started							
4-7 a m	60		1,700	4	32	30	20	14			
4-7 p m			1,425	2	40	26	22	10			
4-8	84 (12 2 gm)	4,500,000	2,800	45	22		24	4			
4/9	74 (10 7 gm)		3,300	18	30	2	28	18	2		2
4/10	76 (11 9 gm)	4,500,000	6,600	62	10		27	1			
4/11	70 (10 2 gm)	3,500,000	5,500	55	18		18	7	2		
4/12	78 (11 3 gm)	4,200,000	5,400	61	13		22	2	1	1 marked toxic granu- lation of neutrophils	

Comment Though the patient had a leukopenia, she was given sulfapyridine for a bilateral bronchopneumonia. Seventeen hours following the institution of therapy, after 6 grams of the drug had been taken, a marked fall in the leukocytes had occurred. Accompanying this was a fall in the hemoglobin.

Discontinuance of the drug, a blood transfusion, and pentnucleotide stimulated the bone marrow, and within three days the number of leukocytes had risen to within normal limits.

This case is apparently the only one on record of the occurrence of a leukopenia following sulfapyridine after so short an interval (17 hours)

DISCUSSION

Contrary to the experimental findings of Wein,⁵ Mollitor and Robinson,⁶ and Johannsen and St George,⁷ and the clinical observations of Whitby,⁸ it has been shown by Marshall et al⁹ and Brown et al¹⁰ that sulfapyridine is more toxic than sulfanilamide in comparable dosages. Long et al,¹⁰ experimentally, and Reinhold et al,²⁰ clinically, demonstrated that sulfathiazole is less toxic than sulfapyridine.

From January 1939 until February 1941, 344 patients received sulfanilamide, 49 neoprontosil, 8 sulfanilamide plus sulfapyridine, 4 sulfanilamide plus neoprontosil, and 2 sulfanilamide plus sulfathiazole in The Bronx Hospital (a general hospital of 300 beds). During this period there has been one case of agranulocytosis and one case of leukopenia following 45 and 43 grams of sulfanilamide respectively. This is an incidence of 0.58 per cent with respect to sulfanilamide alone. From the inception of sulfapyridine therapy in March 1939 until February 1941, 294 patients received this drug, and six sulfapyridine plus sulfathiazole. Agranulocytosis developed in one male and leukopenia in one female following 89 and 6 grams of sulfapyridine respectively, an incidence of 0.68 per cent. Ten patients received a combination of sulfapyridine plus neoprontosil during this latter period. In one patient leukopenia followed the use of 20 grams of sulfapyridine followed by 6 grams of neoprontosil, an incidence of 10 per cent. However, the white count fell following the discontinuance of the sulfapyridine, the fall was hastened during the administration of the neoprontosil and reached its maximum after this drug was discontinued. Fifty-one patients received sulfathiazole between July 1940 and February 1941. None of these patients exhibited a toxic effect on the myeloid elements.

The sulfonamides depress the function of the bone marrow and apparently act mainly by arresting the maturation of the leukopoietic elements.²¹ The erythroblastic elements may also be affected. Arrest of maturation, however, does not fully explain the rapid disappearance of the circulating leukocytes. In acute hemolytic anemia produced by the ingestion of sulfanilamide, most authorities agree that the rapid fall of the erythrocytes and hemoglobin is due to a direct toxic effect of the drug on the circulating red blood cells. The few postmortem observations in this condition have revealed a hyperplastic marrow such as occurs in response to peripheral blood destruction. One may, therefore, postulate that the rapid disappearance of the leukocytes from the peripheral blood may be due in part also to a direct toxic action of the sulfonamides on these cells. The damage to the bone marrow may become manifest as early as one day after administration of the drug or as late as 10 days after its discontinuance. (Briggs in one of his cases reports a granulocytosis as late as 10 days after therapy was discontinued.)

The total dosage, not the blood concentration of the drug, is probably the important factor in producing granulocytopenia. With sulfapyridine there has been as high a blood concentration as 18 mg per cent without a deleterious effect and as low as 5.7 mg per cent with granulocytopenia. Apparently an idiosyncrasy to the drug must exist before the effect on the bone marrow becomes evident. One of us (M S) has given a patient with subacute bacterial endocarditis 104 grams of neoprontosil in a period of 21 days, followed by 335 grams of sulfapyridine in the next 98 days. Another patient with the same disease received 21 grams of neoprontosil in a period of 10 days and 138 grams of sulfapyridine in the succeeding 27 days without any effect on the bone marrow or the disease itself. In the majority of the cases reported where agranulocytosis followed sulfapyridine, the dosage was above 50 grams, with a range of 18–95 grams^{13, 14}. For agranulocytosis following sulfanilamide, the dosage has been between 40–50 grams with a range of 15–90 grams^{15, 16}. In our series of cases leukopenia followed the ingestion of 65 grams (4.3 grams) of sulfanilamide in one case, and 6 grams of sulfapyridine in another. (The lowest dosage previously reported for a leukopenia following sulfapyridine was 6 grams¹⁷). In three of the cases of agranulocytosis about 4 grams of sulfanilamide or sulfapyridine plus neoprontosil were taken. Sutherland¹⁸ warns that quantities over 50 grams may be dangerous to patients who are already suffering from a disease which causes some destruction of the red cells. This statement should be modified. Much lower dosages, as pointed out above, can be just as dangerous. It also should be emphasized that leukopenia or agranulocytosis, just as hemolytic anemia or toxic hepatitis, may appear within 24 hours of the inception of sulfonamide therapy.

The frequency and seriousness of this complication may be surmised from the finding that in the borough of The Bronx, with a population of about 1,600,000, there were 12 deaths (practically all the cases were due to sulfanilamide) from agranulocytosis following the administration of the sulfonamides between 1938–1941.²¹

SUMMARY AND CONCLUSIONS

Six cases illustrating the toxic effect of the sulfonamides on the myeloid elements have been presented. Three have been due to sulfanilamide, two to sulfapyridine, and one to a combination of sulfapyridine plus neoprontosil.

Two cases of agranulocytosis followed the use of 4 and 45 grams of sulfanilamide given over a period of one and 21 days respectively. The patients did not respond to therapy and apparently died of the blood dyscrasia. One case of leukopenia developed after 65 grams (4.3 grams) of sulfanilamide given over a period of 24 hours.

Following sulfapyridine therapy, one patient developed a leukopenia after the ingestion of 6 grams over a period of 17 hours. In another patient, 89 grams of the drug taken over 17 days resulted in agranulocytosis. This

condition did not respond to therapy and apparently hastened the patient's demise

Twenty grams of sulfapyridine plus six grams of neoprontosil taken over a period of 14 days, caused a leukopenia in another patient

Two probable cases of agranulocytosis following sulfanilamide and neoprontosil therapy have also been presented Both patients received about 3.5 grams of the two drugs One of the patients expired and the other recovered

From January 1939 to February 1941, 768 patients received sulfanilamide and its related compounds in The Bronx Hospital Five exhibited a toxic effect on the myeloid elements, an incidence of 0.65 per cent (Cases having received the drug before entry to the hospital are not included in the statistics¹)

Certain conclusions may be drawn from the cases presented

We are dealing with drugs that have a definite toxic effect on the bone marrow, hence they should be used only when there is a definite indication Promiscuous use for minor ailments, such as mild respiratory infections, tonsillitis, gripes, etc., is to be condemned

Frequent blood examinations should be done not only while the drug is being given, but for 5-10 days after it has been discontinued

The dosage of the drug, not the blood concentration, is probably the factor that determines whether a toxic manifestation will occur in a susceptible individual

Although a small dose may cause leukopenia or a fatal agranulocytosis (4 grams in two of our cases), these toxic effects on the bone marrow usually manifest themselves after prolonged use, especially in instances where the disease itself has a deleterious effect upon the hemopoietic system

In view of the incidence of the more severe manifestations of the sulfonamides we feel that one is seldom justified in using these drugs prophylactically

- 3 KRACKF, A R, and GARVER, E C Diseases of the blood and atlas of hematology, 1937, J B Lippincott Company, Philadelphia, p 141
- 4 GROF, J, and GELBERMAN, C J Agranulocytose (maligne Neutropenie) door Duc Genesmiddelen, Nederl tijdschr v geneesk, 1934, lxxviii, 3444
- 5 WEIN, R The toxicity of 2-(p-aminobenzene-sulphonamide-pyridine), Quart Jr Pharm and Pharmacol, 1938, vi, 217-224
- 6 MOLITOR, H, and ROBINSON, H Acute, cumulative and chronic toxicity of sulfapyridine, Arch Internat de Pharmacodyn et de Therap, 1938, lxi, 281-294
- 7 JOHANNSEN, H W, and ST GEORGE, A V Toxicity and therapeutic effect of sulphapyridine in animals, Am Jr Clin Path, 1939, ix, 414-420
- 8 WHITBY, L Chemotherapy of bacterial infections, Lancet, 1938, ccxxv, 1095-1103
- 9 MARSHALL, E K, JR, BRATTON, A G, and LITCHFIELD, J T Toxicity and absorption of 2-sulfanilamidopyridine and its soluble sodium salt, Science, 1938, lxxxviii, 597
- 10 BROWN, W H, THORNTON, A C, and WILSON, J S An evaluation of the clinical toxicity of sulfanilamide and sulfapyridine, Jr Am Med Assoc, 1940, cxiv, 1605-1611
- 11 DOIGOPOL, V B, and HOBART, H M Granulocytopenia in sulfapyridine therapy, Jr Am Med Assoc, 1939, cxiii, 1012-1017
- 12 BRIGGS, G O Granulopenia following the administration of M & B 693, Lancet, 1939, ii, 237
- 13 TZANCK, A, ARNOUS, J, and PAILLAS, J P Agranulocytose mortelle apres administration de p-amino-benzene-sulfanilamidopyridine (693) a doses moderees, Bull et mem Soc med d hop de Paris, 1939, lv, 576
- 14 ROSENTHAL, N, and VOGEL, P Granulocytopenia caused by sulfapyridine in children, Jr Am Med Assoc, 1939, cxiii, 584-587
- 15 GARVIN, C F Complications following administration of sulfanilamide, Jr Am Med Assoc, 1939, cxiii, 288
- 16 SHECKFT, H A, and PRICE, A E Fatal granulocytopenia following administration of sulfanilamide, Jr Am Med Assoc, 1939, cxii, 823
- 17 MORGAN, J R E, and DFTWEILER, H K The hematologic study of 76 pneumonias treated with sulfapyridine including a fatal case of agranulocytosis, Jr Lab and Clin Med, 1939, xlv, 275-281
- 18 SUTHERLAND, M E Agranulocytosis following the administration of M & B 693, Lancet, 1939, i, 1208-1209
- 19 LONG, P H, et al Quoted by BROWN, A E, and HERRELL, W E Clinical experience with sulfamethylthiazole, Am Jr Med Sci, 1940, cc, 618
- 20 REINHOLD, J G, et al Observations on the pharmacology and toxicology of sulfathiazole in man, Am Jr Med Sci, 1940, cxci, 393
- 21 Personal communication with DRS CHARLES HOCHMAN and LOUIS LEFKOWITZ, Asst Med Examiners, Bronx County
- 22 FILLER, W E Puerperal sepsis due to *Staphylococcus aureus* treated successfully with sulfamethylthiazol, Am Jr Obst and Gynec, 1941, xli, 145
- 23 KENNEDY, P C, and FINLAND, M Agranulocytosis from sulfathiazole, Jr Am Med Assoc, 1941, cxvi, 295

THE RESPONSIBILITY OF THE HOSPITAL STAFF IN GRADUATE MEDICAL EDUCATION ¹

By FRANK J SLADEN, M D , F A C P , *Detroit, Michigan*

It is a noteworthy fact that graduate medical education has grown in interest to the extent that responsibility for its careful planning and most effective application is now one of the foremost problems of the medical profession. The demand that educational opportunities be provided for all graduates is an equal partner with the need of making them want them and use them when they are provided. Practice, general and special, need not be criticised for this. For the progress in clinical medicine and in the related basic medical sciences is marching ahead with a rapidity overwhelming to the man who is very busy or otherwise isolated from easy knowledge of the advances.

Life in medicine is a great progressive program of education, in which our ignorance is being constantly revealed to us to our discomfort. As long as no callus of indifference forms to protect us, this discomfort will stir us to further action and prove our safety in the end. A satisfaction with what we have, a lack of desire for more, and little or no interest in the new cannot be overcome by the provision of opportunity alone.

The need of further instruction grows, as the decades dissipate the certainty of things which seemed to characterize the earlier years. These facts make right and proper the plans of continued medical education, now in the minds of so many, and at this time being put to trial in widely separated areas of this country. Further, any outliving way of living, such as the practice of medicine, requires well planned and accessible means of refreshing. Graduate medical education must furnish this as part of what is best in the quality of life in medicine, in a manner, too, which shall redound to the credit of the participating doctor in the eyes of his patient, instead of criticism of him, shall label him as progressive and up-to-date in his community, instead of inadequate, and shall create in him a desire for the opportunity, even a feeling that he cannot afford to miss it, instead of one of satisfaction with what he already knows.

If the seeds of enjoyment of learning have been sown, and the more or less insatiable demand and search for the truth are there, one finds the opportunity to satisfy it present in every hour and every day, and with every patient

If, in turn, one is ambitious to teach and has a real love of teaching, he finds the opportunity every day of his life, whether it be to his patient, his patient's family, the nurse, the student, the industrial executive, his own family at home, or medical students, interns, staff members or older colleagues. The opportunity challenges him every day. It fairly envelops the man in medicine today. The response depends upon him, his natural equipment, upon the examples that have been set him, and his earlier training.

These facts build the picture of medicine as a huge program which is educational by natural evolution. Medicine must expect of its graduate this dual rôle of student and teacher. It should be firmly engrafted in his purposes before graduation. If he is a good student, he has the first point in making him a good teacher.

One must continually seek the truth, and then share it with his colleagues and others, if to their advantage. In medicine it is to our credit to covet the knowledge and skill of the other fellow and work until we get them.

The trend today in all professions, not medicine alone, is toward a conversion of what is traditionally acknowledged as a need for constant study, into real action in the form of search for opportunities to learn and if possible by some reasonable method of concentrated devotion of time and effort. President Ruthven of the University of Michigan has recently pointed out that the universities in recognizing this to be a fact have reached out to meet what they consider a laudable restlessness and urge among their own graduates. Now they are ready to do so for as many of their related community groups as they can serve.

As early as 1934, "this expansion of interest in acquiring new knowledge" was referred to as "part of a world-wide renaissance in adult education which is permeating all phases of life."

Most revealing is the surprising amount of literature upon the subject of graduate medical education. For three decades this has been appearing increasingly. No one at this stage can have a very original idea or plan, so many and varied and thorough are the articles on record. One can express the situation only as he speaks of the experiences of innumerable enthusiasts, men, and groups of men, who have given themselves to the project.

With state and county societies taking up the cudgel, besides here and there conspicuously an interested leader in medicine, certain national associations and a number of foundations have found it a field for surveys, reports, planning and experimenting. All of these merit careful study, especially the plans of certain foundations to improve medical practice in local areas. Then, too, awareness is necessary, because the already established mechanisms and relationships should not be upset too radically. Regulatory plans

do not supply the need. The ideal is to inject into what is going on, the spirit of renewed study and sacrifice to make increased knowledge and skill available to patients.

The opinion has been expressed that this literature is not read by the profession in general. Anyone forced to review the literature on graduate medical education which has been appearing during the 40 years of this century will be amply repaid. For this review gives substantial foundation and background to any thoughts expressed today, to the suggestions and convictions or results of experiments which furnish answers to this whole problem.

The field least adequately handled, or even considered, in relation to graduate medical education, is that expressed by the title of this paper, the responsibility of the hospital staff.

Medical schools and universities must be the fountain-head for matters pedagogical in medicine. Those who are devoting their lives to teaching must be respected for their greater knowledge in the educational field, even though there is a group who are more devoted to the content of their special field than they are to ways and means, methods, and values involved in the general problems of teaching.

The interest and time of medical school and university hospital staffs and their available funds are said to be taken up with the responsibilities of undergraduate medical education, with the exception that graduates of promise are carried along in opportunities of advanced study and research. This is the group out of which the future teachers and university leaders come. In spite of their full schedules, the majority of university hospitals throughout the country are now giving medical courses for postgraduates at certain times of the year.

In one western state the success of the plan was reported not only in the advantages to the practitioner and the practice of medicine, but it was said the "cloistered professor was given a chance to become acquainted with the general practitioner and his problems," the inference being that his teaching improved along practical lines, more in keeping with the needs of the man in practice.

Much has been said of the university hospital in this connection, but the large general hospital, the community hospital with staff large enough to be balanced, has its own particular field of work to perform. Because it is not a university hospital, it is often called a non-teaching hospital. Many influences in the last 25 years, external and internal, have developed teaching in it as a necessary part of staff training, of clinical programs and of bedside and laboratory work. The reference to it as a non-teaching hospital today means that it is not a university hospital in close relation to the medical school. The staff of the hospital values relationship with the university and medical school, realizing that what the latter prizes most in standards and qualifications the hospital staff wants most to have. One who has lived

through the life-time of such an institution from its beginning 26 years ago to date, can testify to the high purposes and ideals behind its inception and growth, built as a community hospital, organized for service to a city, with the emphasis on standards of care, teaching of staff, and research, as being those influences which interact to produce the most progressive work, the greatest happiness in the work and the best results. If such a hospital is not equipped and qualified to share in some way in the needed graduate teaching, then the first responsibility is to convert it so that it may do so and can be said to have a professedly teaching staff.

Let us see what such a hospital staff is doing today to justify what has been said. Very few staffs of 150 or more are without a nucleus of members who have taught in medical schools in earlier years. They will always have the love of teaching in their hearts. They still have the urge to demonstrate clinical examples somewhat in the happy style exemplified by Osler, or to make an operating pavilion somewhat as impressive as did Halsted, or even to illustrate a pathological demonstration somewhat as vividly as did Welch.

There is little need for external influences to lead such a group to study and to apply the best methods of teaching an intern curriculum, to make maximum use of clinical material for the training of individual members, to pick up with renewed enthusiasm the emphasis upon basic medical sciences in seminars, in special group meetings, in personal thinking and in the analysis of individual cases.

It should go on record that such an institutional staff includes teachers who are keeping in close touch with their colleagues in academic circles and profiting by the opportunity. Such a hospital chooses for its intern the graduate who wants to learn, and then strives in teaching him to develop further his teaching qualities first brought to the fore in his medical school days. The internship thus becomes the second phase of this student-teacher life in medicine.

The activities of such a hospital staff in graduate medical education are both intramural and extramural. The intramural program is built about the staff in training, men who remain one to five years.

In these years, the aim is to develop a spirit in the man and a relationship in the hospital which will form the basis of the extramural program later. In the man, it is the spirit of study and of search for the truth, in the hospital, the providing of opportunities.

Again we should like to emphasize the continuous, educational character of life in medicine, wherein the pre-medical and medical school days form the first phase, the intern and resident years form the second phase, and the life-long era of practice of medicine, general or special, forms the third phase.

The possibilities of continued medical education through the years after graduation are first determined by the type of applicants admitted to medi-

cal schools. During the years of instruction in basic medical sciences and clinical subjects, medical schools are even more responsible for the definition of the limits of later education. The quality of the teaching and of the examples set enables some schools to send out men with the vision of continual striving and study toward that goal of perfection which is never reached, whereas from others the graduates are more inclined to be guided by the one idea of getting to practice by the shortest possible route. Those qualities must be part of him at graduation which make him enjoy the life of a student and look forward with the expectation of living it out in the next two phases of his medical work, in the hospital and in his practice. This is a crucial point for graduate medical education which needs more consideration and pressure. Otherwise it is a despairing task to try to develop this spirit later. The exception may be in those men who seem to find themselves and life's values so much more clearly in the years of hospital training. This usually does not arrive during intern year. It is an experience peculiarly of the third year, during the residency, and some evidence suggests it is related to the way in which responsibilities are placed upon him at this time. Osler says "To his five senses he must add two more—the sense of responsibility and the sense of proportion." These are frequently acquired at this time, and a new man emerges.

So the hospital shares with the medical school the responsibility for nurturing and developing these factors, upon which it is fair to believe post-graduate medical education depends for its successful building.

If the need of the medical school phase is fulfilled, the challenge of the next period must be accepted by all hospitals that appoint young graduates to their staffs, because they are the core of their intramural, teaching activities.

Our experience is clear on this point—if these qualities of continued study and ability to share and impart knowledge, what we have called in this paper the student-teacher qualities, if these are further nourished and kept alive during his year or years of hospital internship and residency, we have every reason to expect this man to carry on as a serious participant in graduate medical education in the years of practice, whether general or special, wherever he is, in the larger city or in the relatively isolated, rural districts.

The how of this accomplishment during intern and resident years is not nearly as important as the spirit behind the how, the adherence to this principle and to this objective, in all the various plans in use for the training of interns and younger staff men.

Throughout the first year, demonstrations and discussions, and emphatically not didactic lectures, are the program. In the spirit of the teaching, "there is no appreciable difference between the teacher and the taught—both are in the same class, the one a little more advanced than the other." The interns are made familiar with the laboratory methods in vogue in the

hospital, the history taking procedures and general and special examinations used, the diagnostic and therapeutic techniques employed, the business of floor administration, emergency states and their handling, the special classes of medications found most useful, the place of physical therapy, medical ethics, customs and courtesies, and the medical economics of the institution and of practice. Procedures are followed through so that it is known that each man has had each experience at least once under supervision. In all clinics, section meetings, special seminars, and so on, the junior men are the focus of teaching. Residents learn much by supervising and teaching interns. Each man is expected to create his own record of his instruction and experience. In this way he is very possessive of his knowledge. It is part of him. Whereas if typed outlines and a syllabus are issued to him, he is apt to store them away in a top drawer without knowing their contents and yet comfort himself with the thought he can get them again when the need arises. The aim is to stimulate the need of personal effort to get and to have and even share with others. For this is the very essence of the habits of continuance.

Osler has summed up the picture in his essay, *The Student Life*: "the hardest conviction to get into the mind of a beginner is that the education upon which he is engaged is not a college course, not a medical course, but a life course, for which the work of a few years under teachers is but a preparation."

It has been said: "While many things are studied, few are studied thoroughly. Men will not take time to get to the heart of a matter. After all, concentration is the price the modern student pays for success."

This is the challenge of the resident years and by making assignments to smaller groups, subsections with more limited fields, after intern year, they have the association with men who show them what it is to delve deeper into clearer understanding of backgrounds and underlying conditions. When clinical medicine, so easily handled in the main without it, has the door opened constantly to the values of the underlying anatomical, physiological and biochemical values, understanding replaces strained memory, and the possibilities of complacency dominating the spirit are dispelled.

Most fortunate are the general hospital staffs that prize a close relationship to a medical school and university. Our residents and younger assistants may register in the graduate department of the University of Michigan and accumulate credits for advanced degrees thereby, while the major part of their work is research in the hospital leading to a final thesis. By this plan, recognition is given to the quality of work of the staff as well as its ability to teach. It is beneficial for both student and hospital.

There is no doubt the residents bring something back from the university which contributes a certain academic character to the conduct of medicine—is stimulating, is making a better clinician of the man, and enhances the efforts of the staff in general. It is by all means the advisable plan, and it

would be a great stimulus and a step ahead if universities would make such hospital staffs or selected members of it an allied, second line of resource in the great field of graduate medical education. For such men in one hospital have already taken over the second phase of training of enough men from different medical schools to approximate (if they all came from one school) one-quarter of the annual graduates of that school. With such hospitals now carrying that responsibility in the training of interns and residents, it cannot be denied that they are playing a large part in the continuance of education of the graduates of all medical schools. Certificates of service plus university credits under this plan will represent much more than just necessary time put in.

The extramural activities of the hospital staff in this field in the State of Michigan are fortunate to be under the wise and untiring leadership of Dr. James D. Bruce, now President of the American College of Physicians. With very evident enthusiasm, university and medical school faculties, members of the state and county societies, and especially of the hospital staffs have joined to provide useful courses in teaching centers, as well as to bring education along practical lines to the man who cannot afford in time or money to go any distance to get it. Dr. Bruce has furnished vision as a pioneer and unusual organizing ability to bring these plans to successful accomplishment.

We have referred to the third phase of the continued medical education as that coming during the years of practice, general or special. A plan has evolved from the impressions gained during a reunion of ex-staff members of the hospital. The surprising spirit of enthusiasm and regard which brought men back from considerable distances, and the enjoyment of sharing the institution and its work again with them showed the existence of an attachment that immediately suggested an unfulfilled obligation on the part of the hospital staff.

Since then, the plan has been unfolding which would cover for a lifetime much of the problem of graduate medical education for an increasing number of doctors in practice.

With 50 or 60 men leaving the staff each year, after one to three or five years' service, the effort has been to tie in with them in their new fields sufficiently to keep alive their friendships with the staff and their feeling that the hospital is a continued source of supply to them even in their absence. This has had nothing to do with the reference of cases, because these men have scattered over the widest areas of the nation and world. Special efforts are made to send them copies of detailed reports of clinics, copies of literature, reviews of section meetings, case reports illustrating new advances in any line, especially therapy, autopsy reports, case reports brought up in clinical pathological conferences, reports brought back from meetings attended, and specially prepared material, if of special benefit to them.

A perfect stream may go forth from men whom they know and who in turn know their needs and speak their language

This is capped by devoting a weekend, once a year, maybe twice, to a program wherein the current work in the hospital is shared and these men are lived with on a basis of friendship and needs. This plan has stirred the enthusiasm of the hospital staff. It has met a fine reaction on the part of the ex-staff members. The opportunities are supplied in a manner which is natural and consistent with the self-respect of the doctor and his standing in the community. Instruction comes from men who know him on a basis already established, men who are aware of the spark, the interest, the hunger, the need of this particular individual. The maximum can be accomplished in this personalized way to prevent mental, moral and physical death of the individual. Each hospital in turn can have the realization, that, in this great plan of continued medical education, it is taking its share of responsibility, and most peculiarly fulfilling an obligation that is its very own.

CASE REPORTS

THROMBOCYTOPENIC PURPURA ASSOCIATED WITH DISCOID LUPUS ERYTHEMATOSUS AND RENAL GLOMERULAR CHANGES¹

By MORTON H. EDELMAN, M.D., *New York, N. Y.*

THE occurrence of thrombocytopenia associated with lupus erythematosus has been referred to by Templeton,¹ Lyon,² Baehr, Klemperer and Schiffrin,³ Ginzler and Fox,⁴ Keil,⁵ and others. However, it had been previously observed by Libman and Sachs⁶ in the second of the four cases, which they reported in 1924 and which for want of a better name, they called atypical verrucous endocarditis. Up to the present thrombocytopenia and the accompanying thrombocytopenic purpura have been considered by many one of the visceral or systemic manifestations of the disseminated form of lupus erythematosus. Further, the chronic fixed variety of lupus erythematosus has been considered non-fatal unless an acute exacerbation with dissemination of skin lesions occurs. It is, therefore, of special interest that the present case report with necropsy findings presents an instance of the co-existence of acute thrombocytopenic purpura, discoid lupus erythematosus, and renal glomerular changes.

CASE REPORT

Clinical History J. R., a 49-year-old salesman, entered the hospital October 24, 1939 acutely ill. He had begun to suffer from thrombo-angitis obliterans of the lower extremities at the age of 34. The chief symptoms had been cramps in the legs and feet, with swelling of the ankles, particularly in the spring and fall. Treatment by physical methods and exercises had been followed in recent years by disappearance of many of the complaints referable to the lower extremities. Appendectomy was performed at the age of 42. A chronic skin condition of the face was known to have been present for two years.

In September 1939, he began to experience frequent epistaxis, slight bleeding from the ears, ecchymoses of the arms and legs, soon followed by severe frontal headaches, dyspnea on exertion with palpitation, and weakness. Then for 10 days there was repeated diarrhea with tarry stools and hematemesis, followed by progressive weakness, dizziness, and pallor. The diet had been poor in meat, bread and butter and excessive in spicy foods.

Physical Examination On admission the temperature was 100° F, pulse 108 per minute, respirations 20 per minute, systolic blood pressure 120 and diastolic 70 mm of Hg. The patient appeared extremely ill, pale, and dehydrated. There was dyspnea at rest and marked restlessness. There were many small and large ecchymotic spots over both arms and legs.

Over the temporal and malar areas of both sides of the face were patches of

* Received for publication February 27, 1941.

From the Department of Medicine, Jewish Hospital, Brooklyn, New York, Service of Dr. E. L. Shlevin.

typical discoid lupus erythematosus These areas were reddish scars, denuded of hair, infiltrated, depressed, atrophic, with adherent scales and many patent follicles

Ophthalmoscopic examination showed pallor of the optic discs but no other abnormalities The lungs were clear The heart was not enlarged to percussion The heart sounds were of fair quality and regular in rhythm An apical systolic murmur was heard On abdominal examination the liver and spleen were not palpable The pulsations of the dorsalis pedis vessels were absent but the pulsations of both posterior tibial vessels were fairly strong

Course in the Hospital October 29, 1940 Fever ranged between 99° and 102.4° F Small amount of blood streaking found in the sputum and in the nasal discharge

TABLE I
Laboratory Findings on Admission—October 24, 1940

Hematological	Chemical Examination of the Blood	Urine
Hemoglobin—37%	Urea nitrogen—22.0 mg %	Specific gravity—1.010
Erythrocytes—2,170,000	Sugar—88.0 mg %	Albumin—faint trace
Leukocytes—7,500	Fibrinogen—436 mg %	Sugar—absent
Polymorphonuclear neutrophils—54%	Calcium—8.8 mg %	
Band forms—18%	Phosphorus—3.9 mg %	Microscopic—occasional red blood cell
Lymphocytes—22%	Total protein—5.19 gm %	
Monocytes—3%	Albumin—3.45 gm %	
Eosinophiles—2%	Globulin—1.7 gm %	
Basophiles—1%	A/G Ratio—1.98	
Platelets—30,000		
Bleeding time—3½ min		
Clotting time—8½ min		
Reticulocytes—9%		
Prothrombin time—normal		
Fragility test—normal		
Bone marrow—absence of megakaryocytes *		
Blood Wassermann test negative, blood culture sterile, sedimentation rate 70 mm/hr (Westergren)		

* Examination of the bone marrow on postmortem study showed adequate numbers of megakaryocytes A possible explanation for this may be that on sternal puncture a specimen from a very limited area is aspirated and the findings may not be a true representation of all the bone marrow elements

TABLE II

Date	HGB	RBC.	WBC	PMN	Band	Lymph	Mono	Eos	Basophiles
10-24-40	37%	2.17	7500	54	18	22	3	2	1
10-27-40	37%	1.84	7200	66	10	24	0	0	0
10-28-40	40%	2.64	6625						
10-30-40	37%	2.04	8800						
11-2-40	34%	1.85							
11-5-40	37%	1.56							
11-10-40	37%	2.7	8000	50	17	26	6	1	0
11-15-40	25%	1.77							

TABLE III

Date	Bleeding Time	Clotting Time	Platelets	Reticuloc
10-24-40	3½ minutes	8½ minutes	30,000	
10-26-40	6 minutes			
10-27-40	6 minutes	8 minutes	30,000	9% CO.
11- 5-40				56 R
11-17-40	2½ minutes		36,000	

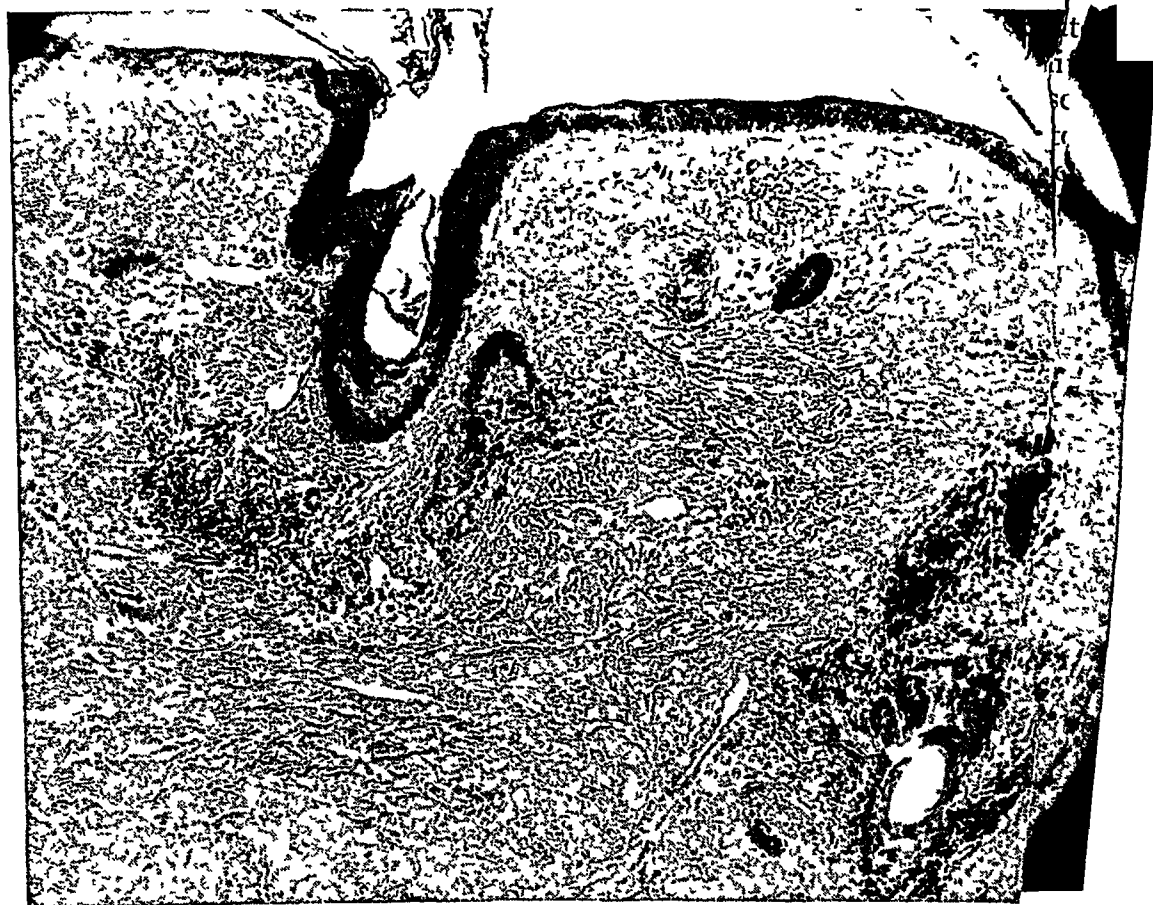


FIG 1 Photomicrograph of section of skin taken from area of discoid lupus erythematosus of the face

November 3, 1940 Several episodes of epistaxis occurred. Temperature ranged between 98.6° and 103° F. Fundus examination showed a few linear hemorrhages. There were numerous ecchymotic spots over the skin.

November 5, 1940 Patient appeared weaker, bleeding from nose and intestinal tract was increased. The platelet count was 30,000 per cm³, the reticulocytes were 56 per cent. Ecchymotic spots appeared on lips, buccal mucous membrane and pharynx.

November 6, 1940 Excision of specimen of skin from area of discoid lupus erythematosus on right temporal region of face showed the following on histological examination:

"One surface is corrugated and is covered by a narrow band of stratified squamous epithelium with keratinizing superficial layers and short blunt rete pegs. The epidermis is flattened out, and the papillae have for the most part disappeared. The vessels within the papillae are likewise few in number. The lymphatics are distended. In the deeper portions, there are focal areas in which there is an infiltration by small round cells, and large mononuclear cells, with occasional plasma cells. Some of these are seen also about blood vessels. There is marked edema of the connective tissue both superficial and deep, and the tissue here has a somewhat basophilic tint. With elastic stain there is marked swelling, fragmentation and clumping of the elastic tissue. Diagnosis: Lupus erythematosus" (Dr D M Grayzel and Dr D L Satenstein)

November 9, 1940 Ophthalmoscopic examination "Media clear, fundi presented general pallor of the optic discs. Disc margins were clear except where obscured by retinal hemorrhages. Veins were tortuous, full and deeply colored. Throughout both fundi there were large, purplish colored linear hemorrhages and small circular whitish exudates, both hemorrhages and exudates were perivascular" (Dr J Levitt)

November 11, 1940 Patient vomited 500 cc dark brown material and small clots of blood. Pulse was weak and rapid. Abdomen was full but the spleen was not palpable. During the ensuing week there was continued intestinal bleeding, fresh and old blood found in the mouth, extreme weakness, rapid, shallow respirations, thready pulse, pallor, lethargy, tenderness and distention of the abdomen. Heart sounds were distant and regular in rhythm.

November 14 to 19, 1940

Blood Pressure	110/64 mm mercury
Temperature	98.6° to 103° F
Pulse	80 to 160 per minute
Respirations	20 to 40 per minute

Nov 15, 1940 Urine examination revealed no abnormalities (specific gravity 1.018). All previous urine examinations between October 31, and November 15, 1940, were normal, the specific gravity ranging between the values of 1.014 and 1.020. The exception was the admission urine specimen which on examination revealed a faint trace of albumin and an occasional red blood cell.

There was onset of hiccoughing which continued periodically until death. The vomitus became grayish. Tongue was covered with old blood. Sclerae became subicteric. Both lungs were clear radiographically.

November 19, 1940 Patient found gasping for breath. Pulse and heart sounds became imperceptible and breathing ceased at 7:30 p.m.

POSTMORTEM FINDINGS

Macroscopic The body was that of a well developed, poorly nourished, white adult male. The skin was pale and there were a few fresh purpuric spots over the abdomen.

There were several small areas of hemorrhage beneath the endocardium of the right atrium and ventricle of the heart. The valve leaflets were thin and delicate. The anterior descending branch of the left coronary artery was tortuous and its distal third could not be traced. There was no evidence of bronchopneumonia. The stomach and intestines were distended with dark blood. There were a few shallow, irregular ulcers in the stomach. There were numerous, irregular, shallow mucosal defects similar to those in the stomach throughout the entire extent of the small bowel. The colon and rectum contained shallow ulcers similar to those in the stomach and small intestines. The gall-bladder contained a solitary, mixed mulberry calculus. The kidneys showed a finely and coarsely granular pale pink surface and were usual in size.



Fig 2 Photomicrograph ($\times 500$ magnification) of a glomerulus showing irregular thickening of the basement membrane and focal endothelial proliferation

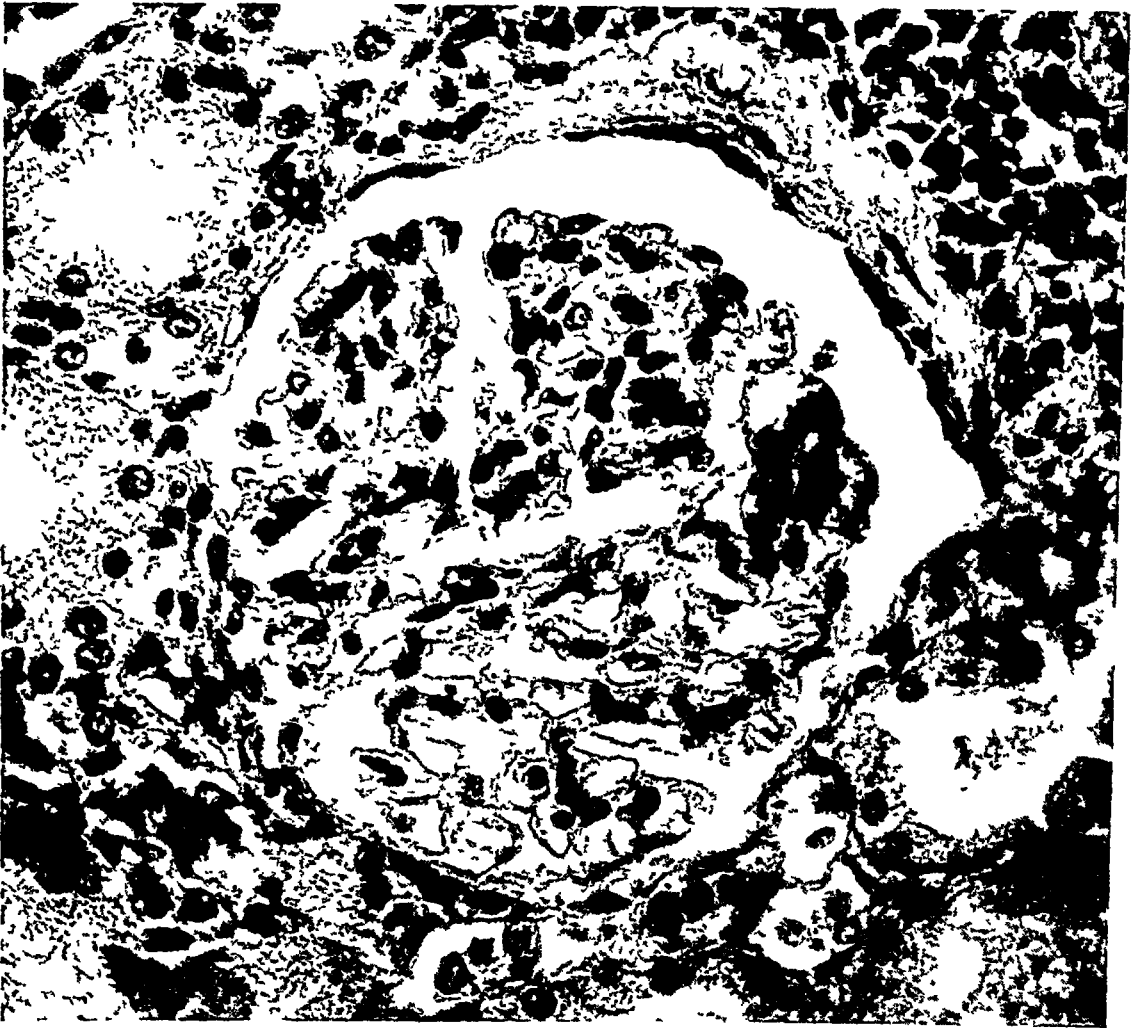


Fig 3 Photomicrograph ($\times 600$ magnification) of glomerulus showing in areas thickening of the basement membrane and endothelial proliferation

The spleen was slightly enlarged. The abdominal lymph nodes were enlarged, soft and discrete.

Microscopic The wall of the right coronary artery was thickened and its lumen was filled with a canalized thrombus. Two vessels at a point beyond which it was not possible to trace the anterior descending branch of the left coronary artery, showed lumina with canalized thrombi. The myocardium showed scattered patches of fibrosis.

The aortic lymph nodes were loosely arranged and contained many large phagocytic and reticular cells.

In sections of the stomach that were taken, none of the ulcers that had been observed were found on microscopic examination. In the small intestine, the mucosa was missing in many places and was replaced by large masses of detritus, containing many small and large mononuclear cells, extending to the submucosa.

There were a few areas of necrosis in the liver and pancreas. There was some hyalinization of the arterioles in the spleen. The kidneys showed definite thickening of the basement membrane in many places resembling "wire-loop" lesions. In places there were evidences of proliferation of the endothelial cells of the glomerulus.

SUMMARY OF THE CASE

The patient, a man 49 years of age, suddenly developed an acute thrombocytopenic purpura. Discoid lupus erythematosus of the face was present and was verified histologically. The anemia was severe and the bleeding uncontrollable. No treatment that was attempted could check the rapidly fatal course of the disease. There was persistent elevation of temperature. The blood culture was sterile. The urine remained clear. The lungs were radiographically clear. There was no evidence of endocarditis. Death was due to hemorrhage and exhaustion.

Autopsy revealed numerous ecchymoses of the skin, the stomach and intestines distended with blood, the spleen slightly enlarged. The significant microscopic findings were in the kidney and consisted of thickening of the basement membrane in places resembling "wire loop" lesions and proliferation of the endothelial cells of the glomerulus.

COMMENT

It is impossible, with our present knowledge of the subject, to prove that the glomerular changes or the acute thrombocytopenic purpura in this case, are visceral manifestations of the discoid lupus erythematosus that was known to exist both on clinical and histological survey. Suffice it to say that both have been described with the disseminated variety of lupus erythematosus and have been considered part of the disease mainly because of the increasing number of cases in which each of the above findings has been observed. Both are important, because if the glomerular changes are visceral manifestations of discoid lupus erythematosus, then additional evidence is brought to bear that the fixed and the disseminated varieties of lupus erythematosus are merely morphologic variants. It is not completely agreed that this is so. Further, if the thrombocytopenic purpura is a manifestation of the discoid lesions that were found, it would necessarily indicate that visceral manifestations of a serious nature may occur with this variety of skin lesion. It has been repeatedly stated that patients with the chronic discoid lesions are not otherwise ill and do not die of the disease. It is well known that the discoid form may undergo acute exacerbation with a dissemination of skin lesions. The associated findings here reported, if they are not coincident, would imply that the discoid form may undergo an acute exacerbation with visceral changes without dissemination of skin lesions.

The renal changes, the so-called "wire loop" lesions, are described in a paper by Baehr, Klemperer, and Schiffrin.⁸ Stickney and Keith⁷ recently reported that in 8 of 15 cases of disseminated lupus erythematosus there was no definite renal change except that seen terminally in debilitating diseases. The most definite lesion that they found was a proliferation of the endothelial cells of the glomerular capillaries, although hyaline thickening of the basement membrane was also frequently present. The arteries and arterioles were found to be normal in most of the cases. The glomerular alterations in the present case were not striking, but positive findings, as suggested by the report of Stickney and Keith, are of significance.

CONCLUSIONS

1 A case of acute thrombocytopenic purpura associated with discoid lupus erythematosus without dissemination of the cutaneous lesions is reported

2 Renal changes consisting of thickening of the basement membrane in places resembling "wire-loop" lesions, and endothelial proliferation in the glomeruli were found at autopsy

Thanks are expressed to Dr M Lederer for reviewing the paper and to Drs E L Shlevin and A Walzer and A Davidson for their kind assistance

BIBLIOGRAPHY

- 1 TEMPLETON, H J Thrombopenia in acute disseminated lupus erythematosus, *Arch Dermat. and Syph*, 1934, *xxix*, 700-702
- 2 LYON, J M Acute lupus erythematosus, *Am Jr Dis Child*, 1933, *xliv*, 572-583
- 3 BAEHR, G, KLEMPERER, P, and SCHIFRIN, A A diffuse disease of the peripheral circulation usually associated with lupus erythematosus and endocarditis, *Trans Assoc Am Phys*, 1935, *l*, 139-155
- 4 GINZLER, A M, and FOX, I I Disseminated lupus erythematosus, cutaneous manifestation of a systemic disease (Libman-Sachs), report of a case, *Arch Int Med*, 1940, *lxy*, 26-50
- 5 KEIL, H Relation between "systemic" lupus erythematosus and a peculiar form of thrombocytopenic purpura, *Brit Jr Dermat.*, 1937, *xliv*, 221-237
- 6 LIBMAN, E, and SACHS, B A hitherto undescribed form of valvular and mural endocarditis, *Arch Int Med*, 1924, *xxviii*, 701-737
- 7 STICKNEY, J M, and KEITH, N M Renal involvement in disseminated lupus erythematosus, *Arch Int Med*, 1940, *lxi*, 643-660

MYXEDEMA HEART, REPORT OF A CASE*

By ARTHUR M MASTER, M D, F A C P, and JENNY STRICKER, M D,
New York, N Y

THE following case is reported because it presented all the typical findings of myxedema heart, which disappeared after thyroid treatment. In addition, the occurrence of pericardial effusion in myxedema heart and its bearing on the symptomatology of the disease will be discussed

CASE REPORT

History B S, a white female of 37, developed the clinical signs and symptoms of hyperthyroidism at the age of 27. The basal metabolic rate at that time was +63 per cent. Following a subtotal thyroidectomy the patient did well until one year ago, when progressive weakness and fatigability became evident. Despite a normal blood count she was treated with liver and iron without relief of her symptoms. Two months prior to observation she had the grippe, which was followed by increased weakness and shortness of breath. She complained of precordial pressure at rest and particularly on exertion.

* Received for publication August 31, 1940

From the Cardiographic Laboratory, The Mt Sinai Hospital, New York City

Examination Physical examination revealed a well developed female. The skin was dry and showed definite loss of turgor. The thyroid gland was not palpable and the healed thyroidectomy scar was apparent. The apex beat was neither visible nor palpable and the heart sounds were of poor quality. The heart rate was 70 beats per minute and the blood pressure 98 mm of Hg systolic and 70 diastolic. There was no evidence of congestive failure.

Fluoroscopy and the roentgenogram (figure 1) revealed a generally dilated, flabby heart which was enlarged to the right and left. The pulsations were definitely diminished and sluggish. This was also seen in the roentgenkymogram. The electrocardiogram (figure 1) showed low voltage of all the complexes and left axis deviation. The basal metabolic rate was —19 per cent. This in conjunction with the other findings suggested the diagnosis of myxedema heart.

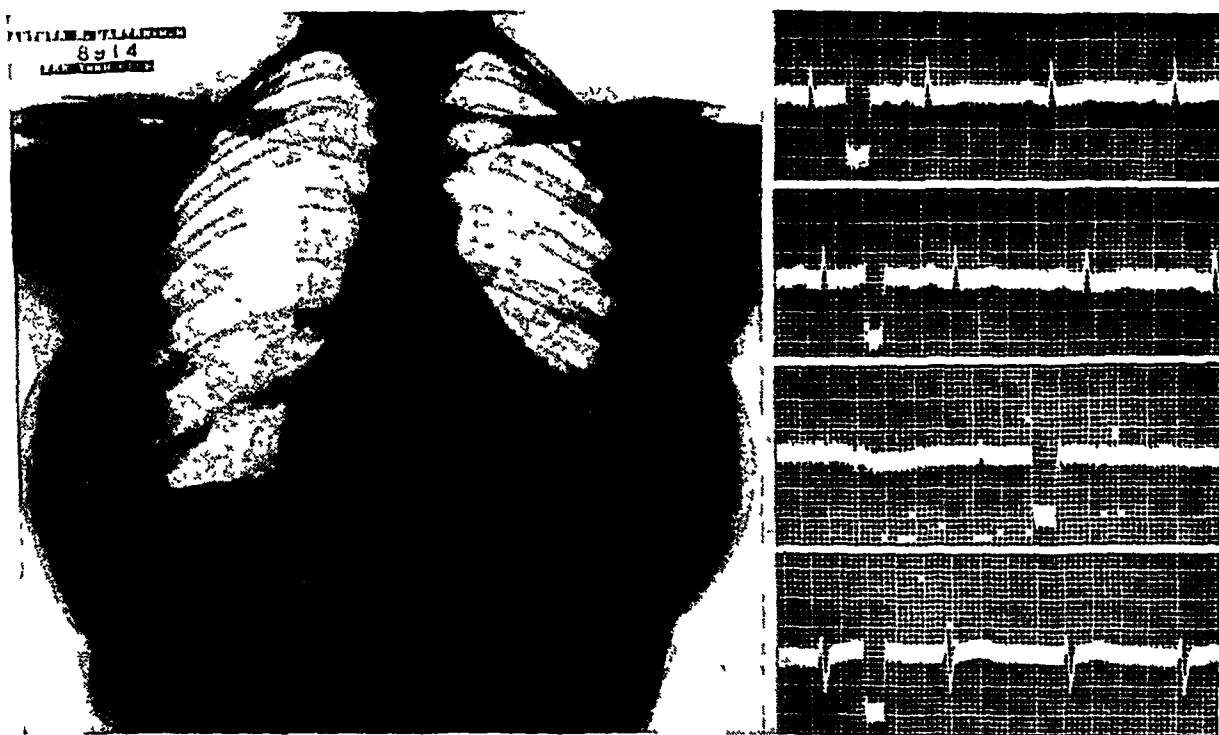


FIG 1 Teleroentgenogram and electrocardiogram before thyroid treatment was begun. Basal metabolic rate —19 per cent. Heart enlarged to the right and left (water bottle shape). The electrocardiogram shows low voltage of the QRS (4 mm) and T-waves.

Clinical Course Thyroid medication, 1 gr daily, was instituted. After 15 days of this treatment the patient was subjectively improved, she was less tired and felt generally better, although there was no change in the basal metabolism or in the electrocardiogram. The thyroid dose was increased to 3 gr daily and within a week the basal metabolism had risen to —5 per cent and the blood pressure to 110/70, and the heart sounds were of better quality. Fluoroscopy and roentgenogram (figure 2) showed a definite decrease in the size of the heart, although it had not returned to normal, the cardiac pulsations were of larger amplitude. In the electrocardiogram (figure 2) the voltage of the QRS and T-waves had increased. The dose of thyroid was then reduced to 2 gr daily to avoid the possible ill effects of overdosage. A week later the basal metabolic rate was —4 per cent and the blood pressure 115/70. The electrocardiogram taken at this examination (figure 3) revealed all the deflections to be of normal voltage and on fluoroscopy the heart was of normal size, in fact it was a small heart (figure 3). The contractions were vigorous. Ten days later the patient

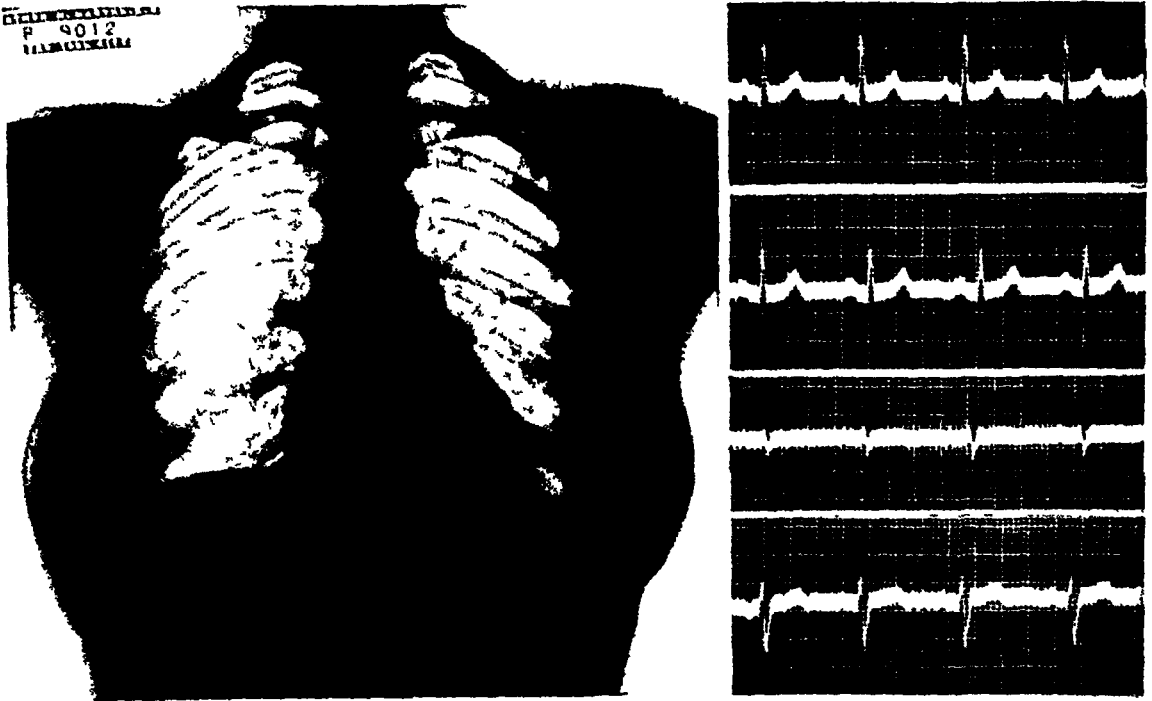


FIG 2 After six weeks of thyroid medication Basal metabolic rate -4 per cent Teleroentgenogram shows decrease of the heart size In the electrocardiogram there is an increase in the voltage of the QRS to 10 mm The T-waves are of normal amplitude There is a slight left axis deviation

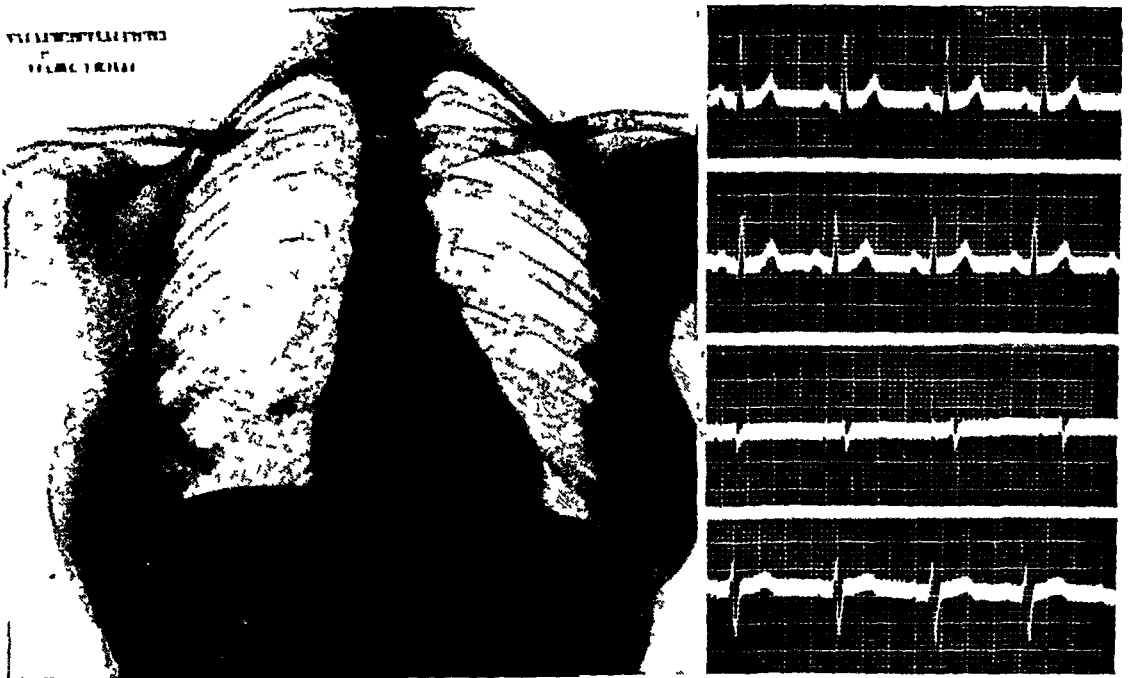


FIG 3 After two months of thyroid medication Basal metabolic rate $+2$ per cent The roentgenogram shows a heart of normal size, and the electrocardiogram a further increase in the voltage of the QRS and T-waves

reported that she was much improved, was very active and complained no longer of any fatigue or weakness

COMMENT

Although it is uncommon to find all the characteristic signs and laboratory evidences of myxedema heart in any single case, our patient was a classical example of this disease. Usually the basal metabolic rate in cases of myxedema is lower than in our patient, yet this diagnosis seems established by the rapid regression of cardiac enlargement and clinical and electrocardiographic improvement following thyroid therapy. Other cases of clinical myxedema with basal metabolic readings of — 20 per cent have previously been reported¹

In 1918 Zondek² was the first to describe myxedema heart as a clinical entity. He reported four unusual cases which presented cardiac enlargement and sluggish cardiac movements accompanied by bradycardia and alterations in the electrocardiogram. He demonstrated the remarkable diminution in the heart size and the return to normal of the electrocardiogram following thyroid administration. Since his original communication ample corroborative evidence has accumulated to justify the term myxedema heart. Assman³ and also Fahr⁴ reported cases of myxedema heart upon which digitalis had no effect. However, when thyroid medication was instituted marked improvement of the myxedema with disappearance of the fluid due to "heart failure" was noted. This is further evidence of an endocrine factor.

The myxedema heart presents a characteristic roentgenoscopic picture. It is triangular in shape and its silhouette bears a striking resemblance to a water bottle. The heart is flabby and its pulsations are sluggish and diminished in amplitude. This is evident on fluoroscopy and can be recorded objectively in the roentgenkymogram, as in the case presented. The electrocardiogram is characterized by low voltage of all the deflections. Following the administration of thyroid the return of the basal metabolic rate to normal is paralleled by a decrease in the transverse diameter of the heart and by an increase in the amplitude of cardiac pulsations and in the voltage of the electrocardiogram. This was well illustrated in our patient by serial electrocardiograms and teleroentgenograms taken during the course of treatment.

The diminution of amplitude of the cardiac pulsations in myxedema has been attributed to a decreased power of muscle contraction. It has been shown experimentally⁵ that the voluntary muscles fatigue rapidly in myxedema and that the fatigue diminishes after thyroid treatment. Apparently the same mechanism holds in the heart muscle, resulting in a decrease in pulsation, which is corrected by administration of thyroid. Formerly, it was thought that the low voltage in the electrocardiogram in myxedema was caused by the increased resistance of the myxedematous skin⁶. However, Thatcher and White⁷ disproved this theory by inserting needle electrodes under the skin without producing any changes in the voltage. The latter increased only after thyroid treatment.

It is interesting to note that the increase in the cardiac silhouette, the diminished pulsations of the heart borders, the low voltage of the electrocardiogram and the very distant heart sounds are also present in pericardial effusion. Several authors therefore have attempted to explain these findings in myxedema on the basis of pericardial effusion and have adduced evidence for this view. In 1927

Goldberg⁸ produced hydropericardium, ascites and anasarca in sheep and goats by total thyroidectomy. More recently Gordon⁹ and Freeman¹⁰ tapped the pericardium in patients with myxedema heart and noted fluoroscopically an immediate decrease in the heart size. The same results were obtained with thyroid therapy, which prevented the re-accumulation of hydropericardium. The effusion recurred, however, when the medication was stopped. Marzullo and Franco¹¹ and Feasby¹² have recently reported similar cases. These observations suggest that the characteristic changes in myxedema heart may be caused by the presence of pericardial effusion. Whether the latter is the direct result of heart failure or an exudative process caused by the myxedema per se is a moot question. The absence of pericardial effusion in the ordinary cases of cardiac decompensation together with the inefficacy of digitalis in myxedema suggests that the pericardial effusion found in myxedema is not caused by heart failure, but by hypothyroidism. One should consider the possibility of myxedema heart in any patient with cardiac enlargement and serous effusions which do not respond to digitalis therapy.

SUMMARY

A case of hypothyroidism is described in which the classical signs of myxedema heart appeared ten years after operation for hyperthyroidism. After six weeks of thyroid medication the patient's general condition improved markedly and all the cardiac abnormalities disappeared. Pericardial effusion is presented as a possible cause for the enlarged heart, the diminished pulsations and the low voltage electrocardiogram in myxedema heart.

BIBLIOGRAPHY

- 1 SCHITTENHELM, A, and EISLER, B. Über die Wirksamkeit des Thyroxins bei endokrinen bedingten Störungen, *Klin Wchnschr*, 1927, vi, 1935
- 2 ZONDEK, H. Das Myxodemherz, *München med Wchnschr*, 1918, lxy, 1180, 1919, lxyi, 6911
- 3 ASSMAN, H. Das Myxodemherz, *ibid*, 1919, lxyi, 9
- 4 FAHR, G. Myxedema heart, *Jr Am Med Assoc*, 1925, lxxxiv, 345, and *Am Heart Jr*, 1927, iii, 14
- 5 FELIX, K. The effect of thyroxine and thyroid extracts on the isolated frog heart, *Proc Staff Meet Mayo Clin*, 1929, iv, 285
- 6 LUEG, W. Ueber das Elektrokardiogramm des Myxodems, *Ztschr f klin Med*, 1926, civ, 337
- 7 THATCHER, C, and WHITE, P D. The electrocardiogram in myxedema heart, *Am Jr Med Sci*, 1926, clxxi, 61
- 8 GOLDBERG, S A. Changes in organs of thyroidectomized sheep and goats, *Quart Jr Exper Physiol*, 1927, xvii, 15
- 9 GORDON, A H. Some clinical aspects of hypothyroidism, *Canad Med Assoc Jr*, 1929, xx, 7
- 10 FREEMAN, E B. Chronic pericardial effusion in myxedema, report of a case, *ANN INT MED*, 1934, vii, 1070
- 11 MARZULLO, E R, and FRANCO, S. Myxedema with multiple serous effusions and cardiac involvement, *Am Heart Jr*, 1939, xvii, 368
- 12 FEASBY, W R. Pericardial effusion in myxedema. Report of a case in which the intrapericardial pressure was measured, *Am Heart Jr*, 1940, xix, 749

AURICULAR FLUTTER OF ELEVEN YEARS' DURATION WITH OBSERVATIONS ON ESOPHAGEAL ELECTRO-CARDIOGRAMS *

By CHARLES E KOSSMANN, M D, and A R BERGER, M D,
New York, N Y

AURICULAR flutter in subjects without other evidence of cardiac disease is usually paroxysmal in type Parkinson and Bedford¹ had five cases of this nature, and Friedlander and Levine had three²

Sprague and White's case³ is unique The patient was a 49-year-old male with auricular flutter which after five years returned spontaneously to normal sinus rhythm Although evidence of heart disease was absent, the aorta was wide and tortuous, and suggested arteriosclerosis

Permanent auricular flutter in otherwise normal individuals is rare Friedlander and Levine² observed for four years one 64-year-old patient who fits into this category Lewis⁴ had a patient whose arrhythmia began at 50 or 53 years of age At the age of 78 years he still had auricular flutter, but in addition showed a right bundle-branch block Of interest was the fact that the rate of the circus which was originally 280 to 300 per minute had slowed to 210 per minute 24 years later There were "no signs of cardiac affection other than flutter" Parkinson and Bedford¹ observed 13 cases of permanent auricular flutter but all had cardiac enlargement without definite etiology The authors say that hypertrophy was probably due to arteriosclerosis and especially to coronary atheroma One of this group, a 61-year-old male (case 31) with bronchitis and emphysema, was first seen in congestive heart failure in 1914 He improved with digitalis, and thereafter failure did not recur despite his refusal to continue with the drug Auricular flutter persisted until the patient died 12 years later

Definite evidence that auricular flutter alone can give rise to hypertrophy of the heart seems to be lacking This is in contrast to the facts regarding auricular fibrillation which apparently can give rise both to auricular⁵ and ventricular^{6, 7} hypertrophy even in the absence of congestive heart failure The present case is reported because it is an example of auricular flutter of unknown etiology giving rise in a young normal subject to hypertrophy of the heart over a period of 11 years, and finally to congestive heart failure Standard, precordial, and esophageal electrocardiograms are discussed because of several interesting features

CASE REPORT

W C, a 38-year-old white truckman, was admitted to Bellevue Hospital in 1924 for serofibrinous pleuritis probably complicating pneumonia The heart was not considered abnormal on physical examination During 1925 the patient first experienced paroxysms of palpitation accompanied by weakness, faintness, dizziness, and dyspnea For these complaints he was readmitted to the hospital in December 1925 and again in March 1926 Clinically the heart was not enlarged The blood pressure was 120 mm Hg systolic and 80 mm diastolic A regular rhythm was interrupted by an oc-

* Received for publication August 24, 1939

From the Department of Medicine, New York University College of Medicine, and the Third (N Y U) Medical Division and Cardiac Clinic of Bellevue Hospital, New York

casional premature systole Auricular flutter was first observed later in 1926 but was initially verified by electrocardiograms in January 1927

There was no history of rheumatic fever, syphilis, or hypertension, and no evidence of these diseases was ever detected during the 13 years he was observed Radial and brachial arteriosclerosis, originally absent, appeared in minimal degree before death The basal metabolic rate was within normal limits Tea and coffee were taken in moderation The patient had been a heavy drinker of alcoholic beverages for many years and would often be intoxicated at clinic visits His diet was adequate, however, in essential foods and accessory factors

During most of the time he was comfortable, and able to carry on his work as a truckman In 1932 he survived a fracture of the skull and of the mandible received in an automobile accident He attended the Cardiac Clinic irregularly, and was admitted to Bellevue Hospital on eight different occasions for study The ventricular and pulse rates were usually between 100 and 120 per minute but could be made slower with digitalis or pressure on either carotid sinus Of interest was the fall in venous pressure that would accompany the latter procedure⁸ Dyspnea, orthopnea, palpitation, pallor, dizziness, and faintness would appear when the ventricular rate was 200 per minute, or over Episodes of this fast rate, which were shown electrocardiographically to be due to 1 to 1 response of the ventricles to the auricles (figure 1 D), occurred at variable intervals and usually persisted for 5 to 60 minutes They were easily terminated by pressure on either carotid sinus, whether the patient was receiving digitalis at the time or not¹

The circus rhythm persisted until the patient's death in 1937 despite all efforts to restore sinus rhythm Among the unsuccessful measures employed were full digitalization (table 1), quinidine to the point of toxicity (table 2, figure 1 E), choline chloride, acetyl-beta-methyl choline, and carotid sinus pressure

TABLE I
Effect of Digitalis on Rate of Circus

Curve No	Time	Mean Auricular Cycle Length in Seconds	Auricular Rate Per Minute	Ventricular Response
8442 (control)	Jan 22, 1927	0.254	236	Irregular (1 2 and 1 3)
(4.8 gm Digitalis given orally in period of 11 days, from Jan 26 to Feb 5, 1927)				
8491	Feb 2, 1927	0.257	233	Irregular (1 2, 1 4, and 1 5)
8495	Feb 5, 1927	0.258	232	Irregular (pre- dominantly 1 4)

Eight teleroentgenograms were made during the 11 years of observation Reports on the significant measurements were available in six, and are listed in table 3 In 1928 the patient weighed 150 pounds and was 65 inches tall The predicted transverse diameter of the cardiac silhouette in a teleroentgenogram⁹ for this height and weight is 12.9 cm, at the time the actual transverse diameter was 14.0 cm or +8.5 per cent The progressive increase in this diameter after 1934 is clear from the table During the entire period of observation the patient's weight did not fluctuate appreciably The largest transverse diameter, 16.8 cm, was obtained in 1937, when he was convalescing from congestive heart failure The aorta became progressively wider, longer, and more tortuous In 1934 a large left aortic arch was seen fluoroscopically

TABLE II
Effect of Quinidine on Auricular Flutter

Curve No	Time	Quinidine in Grams	Auricular Rate Per Minute	Ventricular Response
8521 (control)	Feb 11, 1927		238	Irregular
8562	Feb 23, 1927			
	9 30 a m	0.4		
	10 30 a m		206	Regular (1 2)
	11 30 a m	0.4		
	1 30 p m	0.4		
	3 30 p m	0.4		
	5 30 p m	0.4		
8568	Feb 24, 1927		186	Regular (1 2)
8569	3 00 p m		200	Regular (1 2)
8573	Feb 26, 1927		242	Irregular
	9 30 a m			

Signs of congestive heart failure first appeared in February 1937. Satisfactory response was obtained to rest in bed and digitalis. When the patient was discharged from the hospital for the eighth and last time on July 13, 1937, all objective evidence of cardiac insufficiency had disappeared. Two days later he died at home. The mode or cause of death could not be ascertained. He was 50 years old.

Electrocardiograms

From January 1927 to July 1937 a total of 35 routine standard electrocardiograms was recorded. Additional curves were taken during special procedures. None was obtained during 1932 or during 1935.

When the patient was receiving no medication the auricular rate varied between 232 and 260 beats per minute. The ventricular response was usually 1 to 2 but on occasion was 1 to 1. The most rapid ventricular rate observed under these circumstances was 250 beats per minute (figure 1 D). It was never slower than 110 per minute. The QRS interval was between 0.08 and 0.10 sec, except in 1937 when it was 0.11 sec (figure 1 G). There was no abnormal deviation of the electrical axis.

For long intervals the patient received 0.6 gm of digitalis daily. During these intervals the rate of the circus varied from 232 to 275 cycles per minute though the latter rate was observed only once. The ventricular response was most often irregular and occasionally as infrequent as 45 times per minute. Table 1 shows the characteristic changes after digitalis given in daily oral doses of 0.4 gm. The rate of the circus was unchanged but auriculoventricular conduction was greatly decreased.¹⁰

The effect of quinidine on one of the several occasions it was given is summarized in table 2. The circus slowed to 186 cycles per minute. Once while receiving quinidine the patient developed a 1 to 1 ventricular response. The ventricular complexes were markedly aberrant, measured 0.13 sec in width (figure 1 E), and occurred 200 times per minute. The intraventricular block was attributed to the quinidine. A somewhat similar response of auricular flutter to quinidine has been reported.¹¹

Potential variations of the extremities and of the precordium¹² were recorded on November 19, 1934 (figure 2). The galvanometer connections were so made

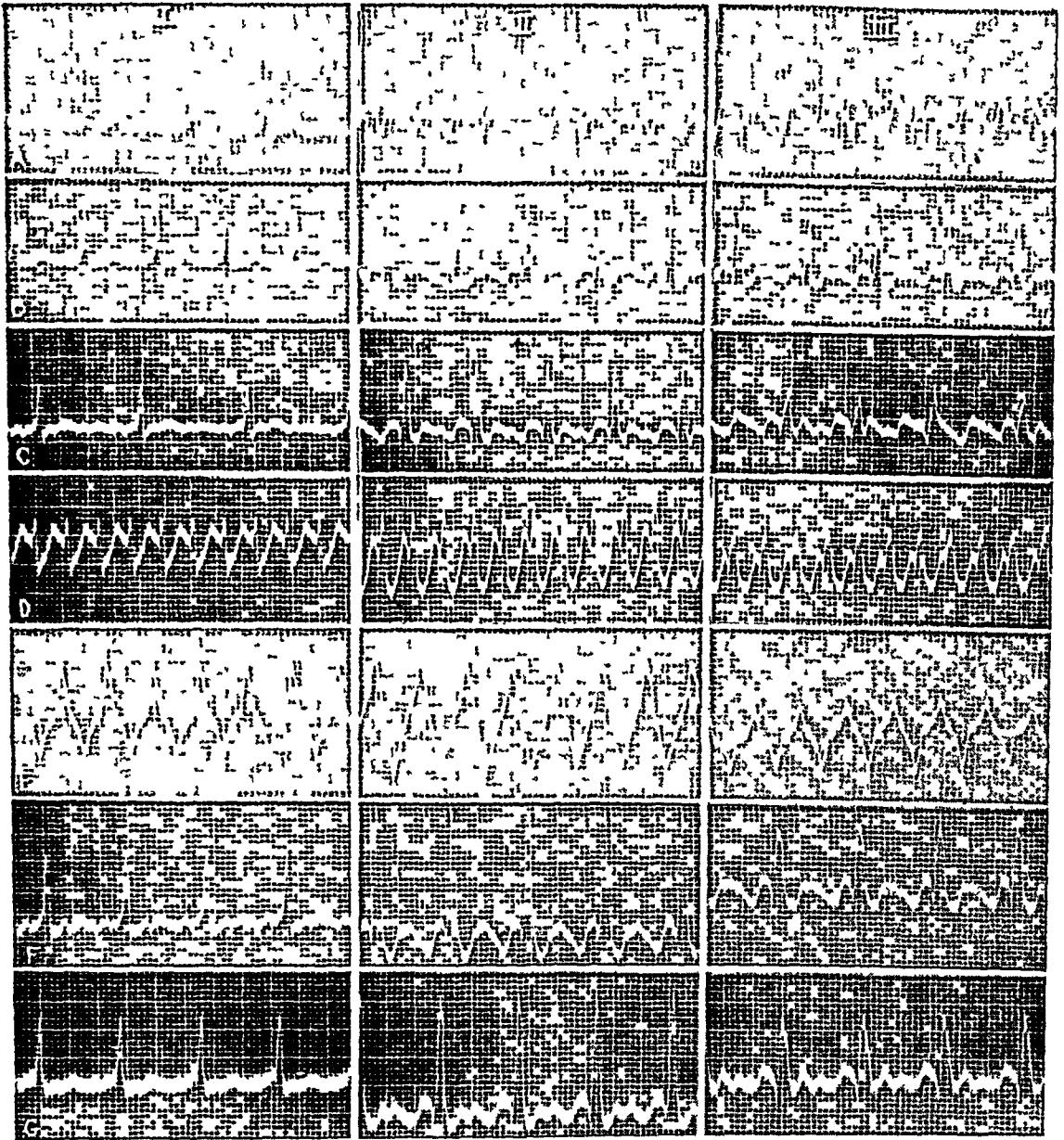


FIG 1 Standard electrocardiograms recorded on the following dates A, 11/14/27, B, 3/16/28, C, 5/12/29, D, 1/26/31, E, 2/13/31, F, 4/28/33, G, 7/7/37. The patient was receiving no medication when A and D were recorded. The latter shows a 1 to 1 ventricular response at a rate of 250 per minute. Curve E also shows a 1 to 1 rhythm but the rate is 200 per minute, and the QRS complexes are aberrant. The patient was receiving quinidine. The remaining electrocardiograms, B, C, F, and G, were recorded while the patient was taking 0.3 gm to 0.6 gm of digitalis daily for long intervals.

that a summit in the record represented negativity of the exploring electrode. The exploring electrode was circular and 1.5 cm in diameter. The curves obtained were not abnormal in any respects.¹³ The flutter waves were largest in the special leads from the right arm (V_R), the left leg (V_L), the right sternal edge (V_1), and the tip of the ensiform (V_E), but they were not more prominent in these leads than in the standard electrocardiograms.

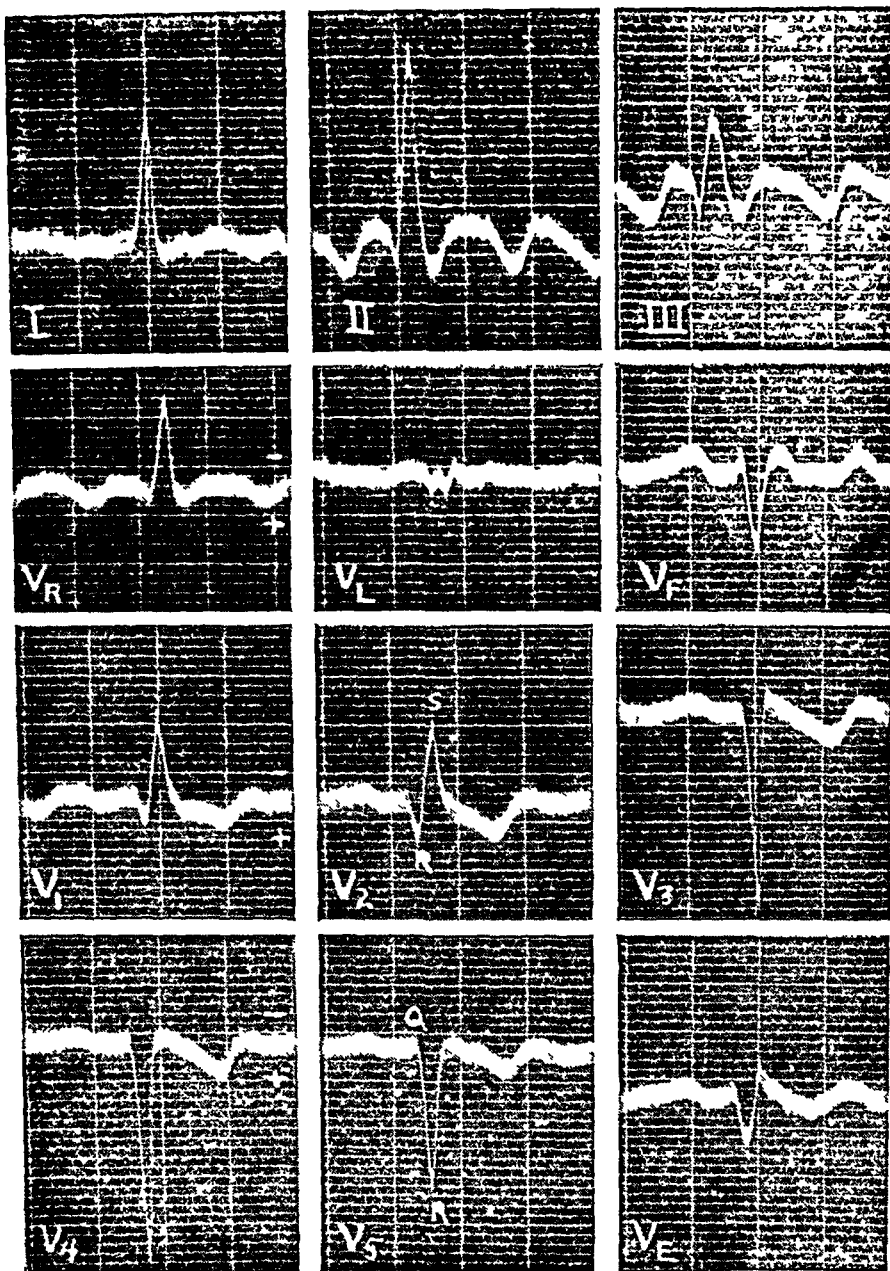


FIG 2 Standard leads (I, II, III) and the potential variations of the right arm (V_R), of the left arm (V_L), and of the left leg (V_E) recorded at normal string sensitivity on November 19, 1934. The last six tracings were recorded at half normal (1 cm = 2 mv) sensitivity, and represent the potential variations of the following precordial points: V_1 , fifth rib, right sternal edge, V_2 , fifth rib, left sternal edge, V_3 , fifth intercostal space, left parasternal line, V_4 , fifth intercostal space, left midclavicular line, V_5 , sixth rib, anterior axillary line, V_E , tip of ensiform. For the special leads a downward deflection represents positivity of the exploring electrode. Therefore, all deflections are labeled as though they were upside down. Time lines occur every 0.2 sec. The patient was receiving no medication.

Esophageal electrocardiograms were recorded on November 19 (figure 3) and again on December 1, 1934 (figure 4). The latter were taken simultaneously with Lead II. The esophageal electrode was a German silver cylinder 2 cm in length and 0.9 cm in diameter. It was connected through the galvanometer to a zero potential electrode.¹² Curves were taken with the esophageal electrode at various distances from the incisor teeth. Those obtained when this distance was 32.5 cm, 37.5 cm, 38.0 cm, and 40.0 cm are shown in figures 3 and 4.

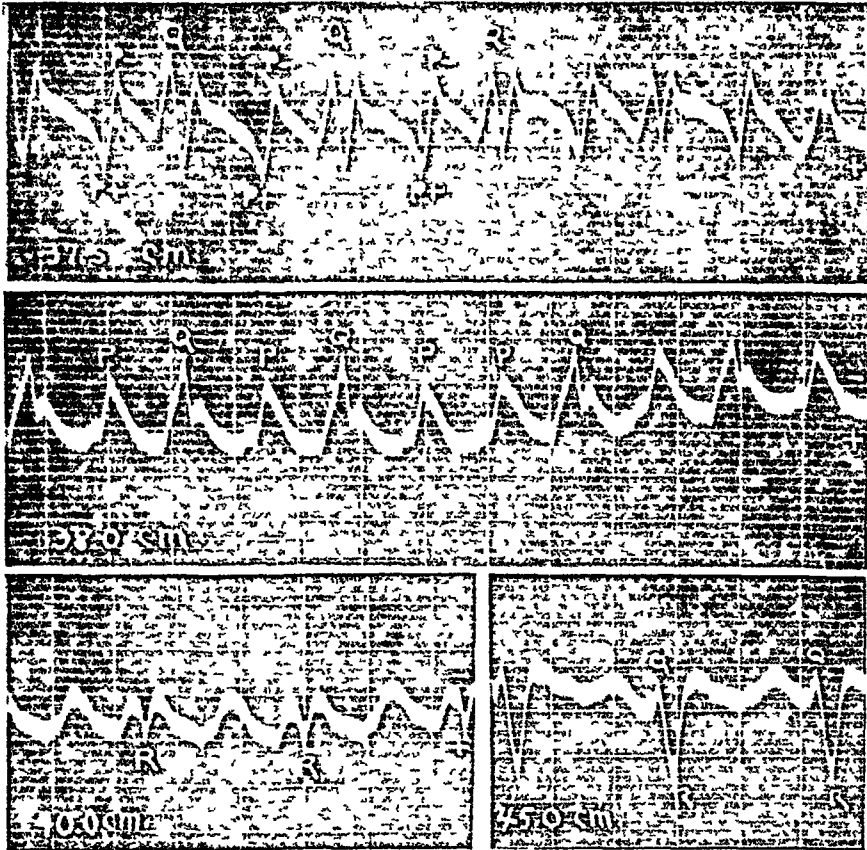


FIG 3 Esophageal potentials on November 19, 1934, at levels 375 cm, 380 cm, 400 cm, and 450 cm from the incisor teeth. The sensitivity of the string is half normal. A downward movement of the string shadow represents positivity of the exploring electrode. Time lines occur every 0.2 sec. Patient was receiving no medication.

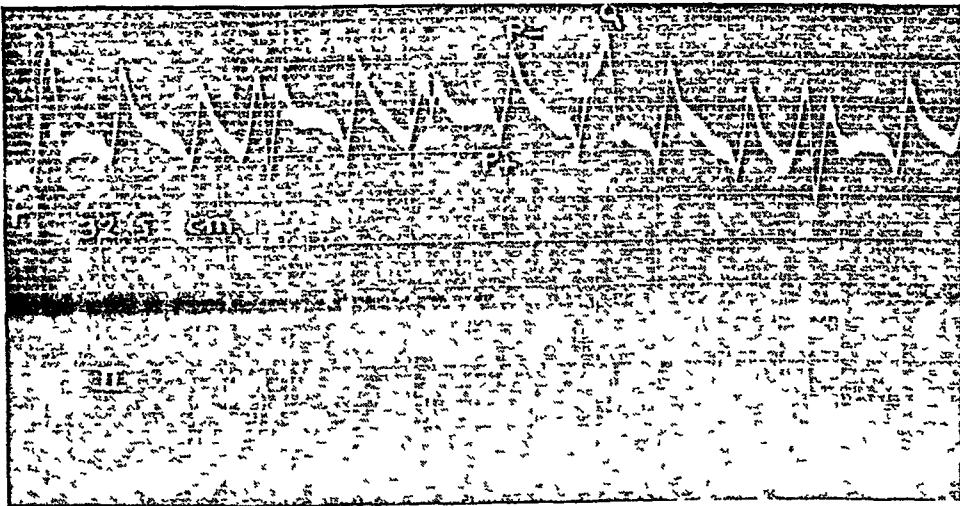


FIG 4 Potential variations of esophagus (upper curve) 325 cm from incisor teeth recorded at half normal sensitivity on December 1, 1934. Standard Lead II at three-fifths normal sensitivity is the lower simultaneous tracing. Time lines, galvanometer connections, and medication, as for previous two figures.

At levels 32.5 cm (figure 4) and 37.5 cm (figure 3) from the incisor teeth the electrode was in proximity to the left auricle as determined fluoroscopically. The P-wave in electrocardiograms obtained at these levels showed an initial, slow, positive deflection (P + in figures) followed by a rapid swing to a negative peak (P -). This descended rapidly at first, more slowly afterward. The positive phase is analogous to the "extrinsic"¹⁴ or pre-intrinsic plus deflection¹⁵ of direct or semidirect leads. The rapid change from positive to negative is similar to the "intrinsic" deflection¹⁴ of direct leads or the intrinsicoid deflection¹⁶ of semidirect leads. The gradually declining negative phase is probably caused by doublets of recovery in the auricle^{17, 18}. This phase is of some clinical importance since it does not appear in the esophageal electrocardiograms of patients with ectopic auricular tachycardia¹⁹, Part II.

It will be noted that the P-wave lost its diphasic character when the electrode was 38.0 cm from the incisor teeth but the ventricular complex still consisted of a single slurred negative deflection as in leads from higher levels. It is labeled Q for the sake of consistency with the nomenclature now used for precordial electrocardiograms²⁰. At the levels under consideration the ventricular complex is negative, probably because the esophageal electrode is opposite the auriculoventricular orifice at the base of the left ventricle. It is, therefore, a semidirect lead from the cavity of the left ventricle which has been shown by Wilson and his associates²¹ to be negative during the greater part of ventricular excitation. The usually negative potential of the right

TABLE III

Cardiac Measurements in Cm of Six Teleroentgenograms Recorded on the Dates Indicated

Date	Transverse Diameter	Width of Aorta	Width of Pulmonic Fields
11/15/28	14	5.2	27.4
5/21/29	13.7	6.1	—
4/20/34	13.9	6.7	26.6
11/15/34	15.2	7.2	28.0
3/27/36	15.9	7.3	28.0
2/26/37	16.8	6.5	27.5

arm in normal subjects has been attributed to the relationship of this extremity to the base of the heart¹⁸. The similarity between the potential of the right arm (V_R , figure 2) and the esophageal ventricular complexes recorded between 32.5 cm and 38.0 cm from the incisor teeth (figures 3 and 4) is to be noted. It is true that the Q-wave of these higher esophageal potentials is simultaneous with the R-wave of Lead II (figure 4), but it is created in a different way. The evidence that this is true is present in esophageal leads taken at 40.0 cm and 45.0 cm from the incisor teeth (figure 3). In these leads the QRS complex is principally a positive deflection, R, preceded in the lead from the lower level by a negative wave or Q. This R is also approximately simultaneous with R of Lead II. This is due to the fact that the esophageal electrode is at these lower levels juxtaventricular and principally on the positive side of the same wave of excitation responsible in large part for the R-wave in Lead II and for the Q-wave in leads from higher levels in the esophagus.

In a semidirect lead from the apex of the heart a ventricular complex similar to that obtained at 45.0 cm from the incisor teeth in the esophagus should be obtained, assuming that the heart muscle displays equal electrical activity in all portions. This is true in the present situation, for Leads V_4 and V_6 (figure 2) are strikingly similar in form to the lowest esophageal lead (figure 3, 45.0 cm).

Evidence that excitation in auricular flutter travels upward in the posterior part of the left auricle was obtained in two ways. First, as the electrode was lowered in the esophagus the initial positive phase (P +) of auricular excitation disappeared

(figure 3, 38.0 cm) and only the negative portion remained. In a sinus rhythm the reverse is true, an entirely positive deflection being obtained from leads more than 40 cm from the incisor teeth.²² This would indicate that in the case under discussion excitation was proceeding in the main away from the esophageal electrode when the latter was at or below the auriculoventricular junction. Second, the time of the auricular intrinsic deflection in esophageal leads at 32.5 cm, 35.0 cm, and 37.5 cm from the incisor teeth was measured with respect to a fixed auricular wave in Lead II. The values obtained respectively were 0.078 sec, 0.094 sec, and 0.102 sec. This means that excitation reached the lowest explored portion of the left auricle 0.024 sec earlier than the highest explored portion. If it is assumed that the esophageal electrode was in or very close to the path of the mother wave of the circus the rate of conduction is calculated at 2083 mm per sec. W. Hurst Brown¹⁰ observed a case of flutter in which excitation took 0.0230 sec to travel between two points 38 cm and 34 cm from the incisor teeth respectively. On the basis of his figures, making assumptions as above, the rate of conduction over this strip of 4 cm was 1739 mm per sec.

COMMENT

Why this patient had auricular flutter remains unanswered. Neither from the history nor from the later structural changes in the heart could the cause be determined. The flutter antedated the appearance of arteriosclerosis. The only possible etiological factor was the excessive use of alcohol, a drug which can inaugurate various cardiac arrhythmias. That alcohol can produce permanent auricular flutter in the absence of organic heart disease is unlikely.

The progressive increase in the size of the heart in the absence of the usually accepted causes of myocardial hypertrophy, and before the onset of congestive heart failure, makes it probable that the abnormal rhythm of the auricles, and the rapid and variable ventricular rate were alone responsible for the anatomical changes observed.

SUMMARY

Auricular flutter of 11 years' duration and of unknown etiology in an otherwise normal individual is reported. Progressive cardiac hypertrophy could be attributed to no cause other than the circus rhythm. Standard and precordial electrocardiograms were not beyond normal limits. Intraventricular block was observed as a toxic manifestation of quinidine therapy on one occasion when the ventricular response to the auricles was 1 to 1. Esophageal electrocardiograms showed that excitation reached the lowest portions of the left auricle earlier than the upper portions. With respect to the ventricular deflections the similarity of an apical lead to a juxtaventricular esophageal lead, and of the potential variations of the right arm to the juxta-auricular esophageal potentials is demonstrated.

The authors express their sincere thanks to the members of the Third Medical Division and Cardiac Clinic of Bellevue Hospital who so diligently collected data and made observations on this case for more than a decade.

REFERENCES

1. PARKINSON, J., and BEDFORD, D. E. The course and treatment of auricular flutter, *Quart Jr Med*, 1927, xxi, 21.
2. FRIEDLANDER, R. D., and LEVINE, S. A. Auricular fibrillation and flutter without evidence of organic heart disease, *New England Jr Med*, 1934, ccxi, 624.

- 3 SPRAGUE, H B, and WHITE, P D Auricular flutter Report of a case of five years' duration with spontaneous restoration of normal rhythm, *Jr. Am Med Assoc*, 1928, xc, 1772
- 4 LEWIS, T Auricular flutter continuing for twenty-four years, *Brit Med Jr*, 1937, i, 1248
- 5 PARKINSON, J Enlargement of the heart, *Lancet*, 1936, ccxlv, 1391
- 6 KAPLAN, B I, CLARK, E, and DE LA CHAPELLE, C E A study of myocardial hypertrophy of uncertain etiology associated with congestive heart failure, *Am Heart Jr*, 1938, xv, 582
- 7 BROWN, M G The relationship of coronary arteriosclerosis to auricular fibrillation with special reference to the term arteriosclerotic heart disease, *New England Jr Med*, 1935, ccxii, 963
- 8 BERGER, A R The value of direct venous pressure estimation in ambulatory cardiac patients, *Am Heart Jr*, 1937, xiii, 440
- 9 UNGERLEIDER, H E, and CLARK, C P A study of the transverse diameter of the heart silhouette with prediction table based on the teleroentgenogram, *Am Heart Jr*, 1939, xvii, 92
- 10 WYCKOFF, J Comparison of digitalis doses in auricular flutter on the auricle and A-V conduction, *Proc Soc Exper Biol and Med*, 1926, lxxiii, 551
- 11 JEZER, A, and SCHWARTZ, S P Unusual manifestations following the use of quimidine sulphate in a patient with auricular flutter, *Am Heart Jr*, 1934, x, 124
- 12 WILSON, F N, JOHNSTON, F D, MACLEOD, A G, and BARKER, P S Electrocardiograms that represent the potential variations of a single electrode, *Am Heart Jr*, 1934, ix, 447
- 13 KOSSMANN, C E, and JOHNSTON, F D The precordial electrocardiogram I The potential variations of the precordium and of the extremities in normal subjects, *Am Heart Jr*, 1935, x, 925
- 14 LEWIS, T The mechanism and graphic registration of the heart beat, 3rd Ed, 1925, Shaw and Sons, London
- 15 WILSON, F N The electrocardiogram in diseases of the coronary arteries Ch XII in Diseases of the coronary arteries and cardiac pain, edited by R L Levy, 1936, The Macmillan Co, New York
- 16 MACLEOD, A G, WILSON, F N, and BARKER, P S The form of the electrocardiogram I Intrinsicoid electrocardiographic deflections in animals and man, *Proc Soc Exper Biol and Med*, 1930, xxvii, 586
- 17 CRAIB, W H A study of the electrical field surrounding active heart muscle, *Heart*, 1927, xiv, 71
- 18 MACLEOD, A G The electrogram of cardiac muscle an analysis which explains the regression or T deflection, *Am Heart Jr*, 1938, xv, 165
- 19 BROWN, W HURST A study of the esophageal lead in clinical electrocardiography Part I The application of the esophageal lead to the human subject with observations on the Ta-Wave, extrasystoles and bundle-branch block, Part II An electrocardiographic study of auricular disorders in the human subject by means of the esophageal lead, *Am Heart Jr*, 1936, xii, 1 and 307
- 20 Standardization of precordial leads Joint recommendations of the American Heart Association and the Cardiac Society of Great Britain and Ireland, *Am Heart Jr*, 1938, xv, 107
- 21 WILSON, F N, JOHNSTON, F D, and HILL, I G W The interpretation of the galvanometric curves obtained when one electrode is distant from the heart and the other near or in contact with the ventricular surface Part II Observations on the mammalian heart, *Am Heart Jr*, 1934, x, 15
- 22 HAMILTON, J G M, and NYBOER, J The ventricular deflections in myocardial infarction, *Am Heart Jr*, 1938, xv, 414

MYASTHENIA GRAVIS; A DISCUSSION, WITH PRESENTATION OF A CASE ASSOCIATED WITH A THYMOMA*

By SAMUEL F. ARONSON, *Camp Murray, Washington*

MYASTHENIA GRAVIS, a symptom-complex manifested by an incapacity of one or more groups of voluntary muscles for sustained effort, is without any demonstrable involvement of the nervous system

Thomas Willis is credited by several authors^{1, 2} with having first described the disease, but Wechsler³ claims that Wilkes in 1877 deserves that credit. Erb¹ gave a clear and classical description in 1878 but believed that the condition was due to pathological changes in the central nervous system. Oppenheim⁴ claimed credit for first clearly differentiating the disease in 1887 and named it bulbar paralysis without pathological lesions. Jolly,² in 1895, demonstrated, by electrical stimulation, rapid fatigue reactions and named the disease myasthenia gravis pseudoparalytica. The disease has also been called Erb-Goldflam disease and asthenic bulbar paralysis. Buzzard,⁵ 1905, described a lymphocytic infiltration in skeletal muscles and this distinctive lymphorrhagia was emphasized by Norris,⁶ and others.

Oppenheim,⁴ in his description of the disease, made the statement "I think it not impossible that in the future the disease may in some cases be cured by the removal of a tumor which is the source of toxic products. Tumors have already been successfully removed from the anterior mediastinum." Weigert,⁶ 1901, was the first to report a case of myasthenia gravis associated with a tumor of the thymus gland. Following Weigert's report, this anatomic relationship has been reported with increasing frequency. Starr⁷ (1912) collected 250 cases of myasthenia gravis for analysis and found enlargement of the thymus in 28 per cent. In 1917, Bell⁸ collected 56 autopsied cases of myasthenia gravis reported after 1901 and found that enlargement of the thymus had been noted in 17 and a tumor in another 10, so that some lesion of the thymus had been found present in almost 50 per cent. Keschner and Strauss⁹ quote Greenfield as pointing out "that negative observations in regard to the thymus are of little value unless the mediastinum has been searched carefully and systematically, since thymus tissue can be readily overlooked in the fat of this region."

In 1936, Norris⁶ added to Bell's series 10 cases, in seven of which thymic lesions were recognized. He stated "I am of the opinion that pathologic changes may be found in the thymus in cases of myasthenia gravis in direct ratio to the care with which they are sought." Alter and Osnato¹⁰ also state that "all cases of myasthenia gravis with definite pathologic observations should be recorded, not only for the reason of their rarity, but that they may serve toward the construction of an explanation of the pathology of the disease, confirm part of it or offer useful hints for future observations." One year after his first report, Norris¹¹ added two more cases to bring his series to 82 cases of myasthenia that came to autopsy. Peer and Farinacci¹² added one case and Miller,¹³ in February of this year, added five more autopsied cases, of which four had thymic lesions. To this group, I wish to add one case, bringing the total of

* Received for publication August 26, 1940

autopsied cases of myasthenia gravis since 1901 to 89, in 43 (48 per cent) of which a lesion of the thymus gland was the outstanding feature

Miller¹³ quotes Lievre as concluding that

- " 1 Tumors of the thymus are frequently found in myasthenic patients
2. Microscopic tumors may easily be missed at autopsy
- 3 There is a definite causal relationship between the thymus and myasthenia gravis and roentgen investigation followed by irradiation or surgical removal is the procedure of choice "

A clearly defined classification of thymic tumors has never been made. Maingolis¹⁴ feels that not only because of the double origin of the thymus but also because of the polymorphism of the cells found, a rigid classification is impossible and that the designation of thymoma for all thymic tumors is the only solution at present. Symmers¹⁵ classifies tumors of the thymic region as peritheliomata, lymphosarcomata, epitheliomata, and spindle-cell sarcoma and has found not only simple hyperplasia of the thymus but also malignant tumors in cases of myasthenia gravis. Ewing,¹⁶ however, classifies tumors of the thymus in association with myasthenia gravis in a category separate from other thymic tumors. Norris⁶ feels that all thymic tumors associated with myasthenia are benign thymomas or adenomas. Bell⁸ found only one possible case of malignancy in his series of 27 thymic lesions associated with myasthenia gravis and over 60 cases of thymic malignancies which were not associated with the disease. Miller¹³ states that Obiditsch studied a series of thymic tumors and concluded that those composed predominantly of small round cells more often were associated with symptoms of myasthenia than were epithelial and malignant types.

Spinal fluid examinations in myasthenia gravis are almost uniformly negative and central nervous system lesions are usually absent. Of various blood disturbances, Noyes¹⁷ states that the most frequent departure from normal is polycythemia (also found in the case cited below). Hart¹⁸ found a marked decrease in sugar tolerance in his own and several other cases (also found in the case cited below). Reports concerning metabolic changes such as increase or decrease of creatine and creatinine excretion are so variable as to lead one to conclude that these changes are independent of the disease itself.

Myasthenia gravis attacks both sexes with about equal frequency. It usually appears between the ages of 20–50 years, although Rothbart¹⁹ cites cases in the same family in which the onset was at the ages of six weeks, three months, and two years. Others have reported the onset at the age of 70 years. The remissions and exacerbations are so characteristically part of the disease as to be included with the symptoms. Headaches, various paresthesias and pains, stiffness of the muscles, and generalized weakness may precede the disease by several months.

The onset is usually insidious although acute infections and pregnancy have sometimes caused abrupt onset of symptoms and Hyland²⁰ has observed that repeated minor infections, emotional stress, hot baths and mild gastrointestinal upsets are apt to cause marked exacerbation of symptoms. Starr⁷ observed in a series of 315 cases that weakness of arms and legs preceded by days to months bulbar symptoms in 38 per cent. Usually, the first noticeable complaint is a diplopia due to weakness of the extrinsic muscles of the eyes or a ptosis due

to weakness of the levator palpebrae superioris. Involvement of the muscles of mastication is of frequent occurrence, as is dysphagia, nasal regurgitation of fluids, dysarthria or aphonia, absence of pharyngeal reflexes and paroxysmal dyspnea. Many of the patients complain of an annoying, stringy mucus. The symptoms are milder in the morning and increase in severity during the late afternoon and evening.

The diagnosis is usually quite easy. The symptoms, the muscular reaction to electricity, the myasthenic reaction to light, absence of muscular atrophy and reaction of degeneration, absence of characteristic changes in deep reflexes, the presence of lymphorrhages in biopsied muscle, roentgenogram finding of a mediastinal tumor, and the prostigmin test all aid in establishing the diagnosis. The Jolly reaction is one where a tetanizing faradic current applied to the muscle of a myasthenic patient repeated at intervals of seconds will cause a very rapid diminution and finally loss of all muscular response followed by recovery after a short rest. The pupils of the eyes show a similar loss of power to rapid stimulation by light. Crosby²¹ states that "A circular, sharply defined, flattened, non-pulsating mass in the anterior wall of the thorax, in the absence of other evidence to the contrary, justifies a tentative diagnosis of probable thymoma." Doub²² gives a good differential diagnosis of the roentgen-ray characteristics of thymus neoplasms from those of other chest tumors. He also describes a technic for deep irradiation treatment. The use of prostigmin as a diagnostic test was first reported by Viets and Schwab,²³ who administered 3 c.c. of injectable prostigmin and gr 1/100 of atropine. This work was confirmed by other observers^{24, 25, 26}. Keschner and Strauss⁹ give an excellent differential diagnosis of myasthenia gravis from various neurological disorders.

The course of the disease is usually progressively downhill despite the use of such drugs as prostigmin. Many cases die within the first year, often of sudden suffocation. However, spontaneous remissions are reported and Laurent²⁷ cites a case of myasthenia gravis with undoubted symptoms for 29 years.

The accepted regime, until recently, was absolute bed rest, abstinence from massage and electrical stimulation, and the use of tonics and glandular extracts. In 1921, D'Amato²⁸ reported marked improvement in a case of myasthenia gravis from the use of epinephrine. In 1930, a short report by Dr. Harriet Edgeworth²⁹ gave new impetus to the treatment. Herself a victim of the disease, Dr. Edgeworth found ephedrine abated the symptoms markedly. Boothby^{30, 31} and others described the use of glycine, advocating five grams of glycine six times daily. Using 10 to 20 mg. per kilo of body weight, Minot and his associates³² treated five cases with guanadine hydrochloride dissolved in normal saline and administered intravenously, obtaining good results in all. Viets and Schwab,² however, were unable to confirm these results.

In 1934, noting the resemblance of myasthenia gravis to curare-poisoning, Walker³³ used physostigmin because of its action as a partial antagonist to curare. Denny-Brown³⁴ suggested the use of physostigmin salicylate orally with belladonna to prolong the good effects and minimize its toxicity. In December 1934, because it was less toxic, Mary Walker began to use prostigmin, demonstrating the results on two cases before the Royal Society of Medicine and reporting her results in February 1935.³⁵ Her results were quickly confirmed by Pritchard,³⁶ Laurent³⁷ and others. Everts³⁸ was the first to report on the oral use of prostigmin, finding it more successful than the injectable variety because of its longer effect and lessened toxicity. He also found that large doses

of potassium chloride augmented the general improvement of the patient, thus confirming the work of Laurent and Walther³⁰ Kennedy and Wolf,²⁶ however, found that some cases became refractory to prostigmin within 1 to 4 months and Harvey and Whitehill²⁵ cited three cases where the early beneficial results decreased with each succeeding injection of prostigmin Hyland²⁰ states that the transient relief is followed by increased weakness and Minski and Stokes⁴⁰ point out that the value of prostigmin is reduced by its toxic manifestations and the difficulty of control in ambulatory cases Simon⁴¹ found that 1 c.c. of anterior pituitary extract given subcutaneously daily gave excellent results in two cases but other observers have been unable to confirm this work

Hsu and Ch'Eng⁴² state that in 1913, Schumacher and Roth reported favorable results in the disease by extirpation of the thymus and that Pierchalla in 1921 advocated irradiation of the thymus as a therapeutic test even when no thymic enlargement could be demonstrated by roentgen-ray Halsted⁴³ stated that when roentgen-ray therapy to the thymus gland was used in cases of Graves' disease that did not get relief from thyroidectomy, prompt and striking improvement was obtained, and stated further that "asthenia, which was common to all the cases, has been particularly influenced" It is my belief that the asthenic symptoms in these cases were myasthenic manifestations and the relationship between thyrotoxicosis and myasthenia gravis should be further investigated

Mella⁴⁴ reported complete recovery followed deep roentgen-ray over the thymus gland in a patient with myasthenia gravis Keschner and Strauss⁹ had two cases that were subjected to roentgen-ray therapy with resulting disappearance of the thymic shadow and a complete disappearance of symptoms Decker⁴⁵ mentions three cases which were treated by thymectomy with good results Hyland,²⁰ using roentgen-ray therapy of the thymus in four cases, obtained marked improvement in two within a short time, slow but continuous improvement in the third six weeks after the last treatment, and partial relief six months after the last treatment in the fourth case (who had had a three year progressive history until that time) Ayer⁴⁶ states that he had one cure due to roentgen-ray therapy of the thymus but gives no details Riven and Mason⁴⁷ report a case of myasthenia gravis with enlargement of the thymus that had several remissions after repeated courses of deep roentgen-ray therapy Thorner and Yaskin⁴⁸ treated three patients without any change from the pretherapeutic state but the amount of therapy was small and the length of observation following treatment was evidently short Miller¹³ recommends irradiation and surgical removal of the thymus in cases of myasthenia gravis

CASE REPORT

Mrs A M W, a white woman, 56 years of age, began to note slight fatigue and malaise in 1938 One year later, she noticed first a twitching, then a drooping of the right eyelid with a transient double vision followed in three months by slurring speech with a nasal tone A decreased sugar tolerance led to a diagnosis of diabetes mellitus and a dietary régime was instituted However, the symptoms progressed rapidly and one week later there occurred a drooping of the jaw, a difficulty in chewing and swallowing, and nasal regurgitation of fluids She also began to experience attacks of dyspnea These symptoms with drooling of saliva were present upon the admission of the patient to the Johns Hopkins Hospital in December 1939 A diagnosis of myasthenia gravis was made and through the courtesy of Dr F R Ford, the following data are recorded

Blood Analysis

Red blood cells	5,420,000
Hemoglobin	110% (16 gm)
White blood cells	7,750
Non-protein nitrogen	30 mg per cent
Calcium	10.4 mg per cent
Cholesterol	177 mg per cent
Basal metabolic rate	plus 12 (satisfactory test)
Wassermann test	four plus
Roentgen-ray	Skull—skull and sella normal
	Chest—negative

Glucose Tolerance Test

Fasting	129 mg per cent
9 30	230 " " "
10 00	287 " " "
11 05	267 " " "
12 05	180 " " "

Guanidine, glycine and ephedrine were all tried but found to be ineffective. Prostigmin did help the patient but was not as successful as in most cases. Small doses of insulin were without any result.

In February 1940, the patient was first seen by me, at which time despite ephedrine gr 3/8 t i d, and 105 mg of oral prostigmin augmented by hypodermic injections of that drug, she was able to take only liquid or pureed foods by painful and slowly swallowed teaspoon doses. She could speak only one or two words at a time, had to continuously hold up her jaw with her hand, complained of an annoying tenacious mucus in her throat and of progressive weakness. The pharyngeal reflex was abolished. Because of the rapid progression of symptoms, the patient was hospitalized on February 20, 1940 at the Swedish Hospital for roentgen-ray therapy. It was planned to administer a total dose of 3000 r over the anterior mediastinum in ten days. Four hours after admission, she received 300 r (200 KV, 2 Cu plus 1 A1, 10 × 10 cm portal, 23 r/minute). The following morning she stated that she felt stronger and, for the first time since the onset, her jaw stayed closed without manual support. However, that afternoon she died suddenly of what appeared to be an acute cardio-respiratory failure. The similarity of this sudden collapse without any cyanosis to that of sudden thymus deaths in babies is most striking. Whether this sudden death 20 hours after the first roentgen-ray treatment is a coincidence or a result is a matter of conjecture.

At the autopsy performed by Dr. D. H. Nickson, the only significant anatomic finding was a retrosternal, encapsulated, somewhat nodular tumor mass (figure 1) adherent to, but easily stripped from, the anterior, upper margin of the pericardium. This mass measured 5.3 by 3 by 1.8 cm and weighed 16.6 grams (Gudernatsch⁴⁹).

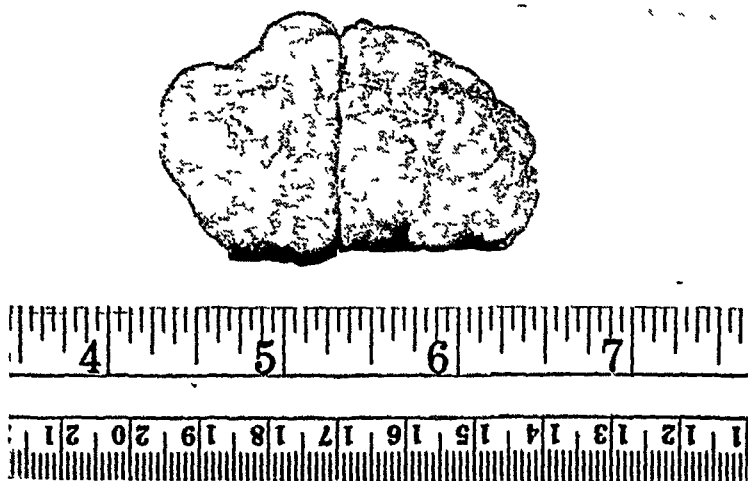


FIG 1 Gross specimen

quotes Hammai as stating that the thymic parenchyma weighs 1.48 grams at 45 to 55 years of age) On the cut section, it was found to be a soft, uniformly gray tumor, somewhat lobulated Microscopic sections (figure 2) revealed fields of small, round lymphoid cells and others where large, pale epithelial cells with clearly defined nuclei and indefinite polyhedral cell borders predominated Less than 5 per cent of the cells showed mitotic figures Scattered throughout were Hassal's bodies. There was a well-defined capsule with trabeculae dividing the gland into lobules but no definite cortex and medulla could be defined



FIG 2 Photomicrograph 200 X

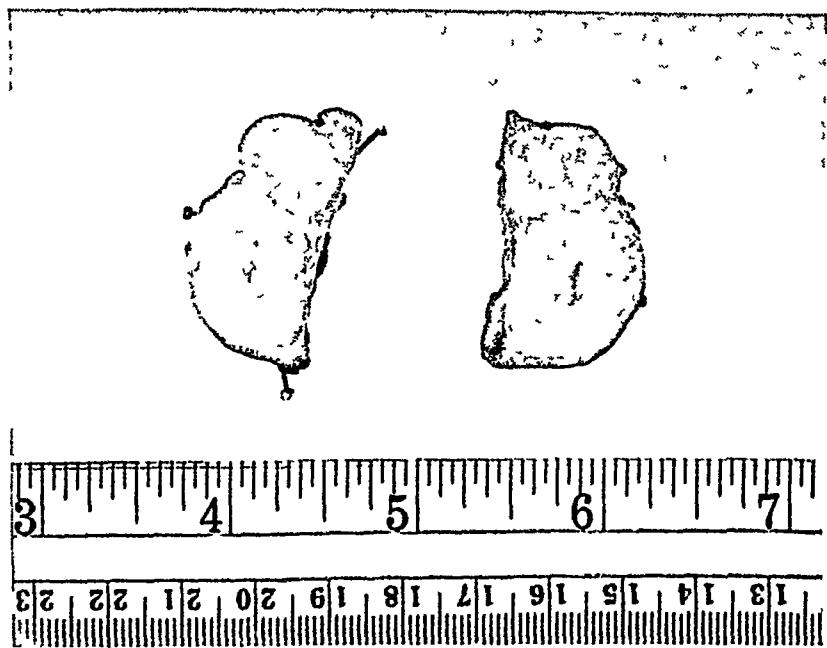


FIG 3

SUMMARY

- 1 A case of myasthenia gravis associated with a thymic tumor is presented
- 2 The etiology and the therapy of myasthenia gravis are briefly reviewed
- 3 The pathology of myasthenia gravis is discussed with particular reference to tumors of the thymus gland
- 4 The literature is reviewed with reference to the treatment of myasthenia gravis by extirpation of or by deep roentgen-ray therapy to the thymus

CONCLUSIONS

- 1 A negative chest film does not mean the absence of thymic enlargement
- 2 Complete roentgenological examination of the chest should be made in all cases of myasthenia gravis, as thymic tumors may be obscured by the heart shadow in the anterior-posterior views
- 3 Where a definite thymic tumor is found by roentgen-ray, extirpation of the gland should be considered
- 4 Deep roentgen-ray therapy should be carried out in all cases of myasthenia gravis even where there are negative chest plates
- 5 Several consecutive roentgen treatments may be necessary and such a course may have to be repeated one or more times before a remission or cure is effected

BIBLIOGRAPHY

- 1 GARRISON, F H History of medicine, 4th Edition, 1929, W B Saunders, Philadelphia
- 2 VIETS, H R, and SCHWAB, R S Diagnosis and treatment of myasthenia gravis, with special reference to use of prostigmine, Jr Am Med Assoc, 1939, cxiii, 559-563
- 3 WECHSLER, I S Text-book of clinical neurology, 3rd Edition, 1935, W B Saunders, Philadelphia
- 4 OPPENHEIM, H Text-book of nervous diseases, Vol 2, 1911, J B Lippincott, Philadelphia
- 5 DAY, A B Myasthenia gravis, recent developments in treatment, report of case, Jr Missouri Med Assoc, 1939, xxxvi, 243-245
- 6 NORRIS, E H Thymoma and thymic hyperplasia in myasthenia gravis with observations on general pathology, Am Jr Cancer, 1936, xxvii, 421-433
- 7 STARR, M A Myasthenia gravis, Jr Nerv and Ment Dis, 1912, xxxix, 721-731
- 8 BELL, E T Tumors of the thymus in myasthenia gravis, Jr Nerv and Ment Dis, 1917, xlv, 130-143
- 9 KESCHNER, M, and STRAUSS, I Myasthenia gravis, Arch Neurol and Psychiat, 1927, xvii, 337-376
- 10 ALTER, N M, and OSNATO, M Myasthenia gravis with status lymphaticus and multiple thymic granulomas, Arch Neurol and Psychiat, 1930, xxiii, 345-360
- 11 NORRIS, E H Thymoma (adenoma of thymus) from unusual case of myasthenia gravis, with observations on general pathology, Am Jr Cancer, 1937, xxx, 308-317
- 12 PEER, G F, and FARINACCI, C J Report of case of myasthenia gravis associated with thymoma, Mil Surgeon, 1938, lxxxii, 350-355
- 13 MILLER, H G Myasthenia gravis and the thymus gland, Arch Path, 1940, xlix, 212-219
- 14 MARGOLIS, H M Tumors of thymus pathology, classification and report of cases, Am Jr Cancer, 1931, xv, 2106-2142
- 15 SYMMERS, D Malignant tumors and tumor-like growths of thymic region, Ann Surg, 1932, xcvi, 544-572

- 16 EWING, J Neoplastic diseases, 3rd Edition, 1922, W B Saunders, Philadelphia
- 17 NOYES, A P Case of myasthenia gravis with certain unusual features, Rhode Island Med Jr, 1930, xiii, 52-59
- 18 HART, H H Myasthenia gravis with ophthalmoplegia and constitutional anomalies in sisters, Arch Neurol and Psychiat, 1927, xviii, 439-442
- 19 ROTHBART, H B Myasthenia gravis in children, its familial incidence, Jr Am Med Assoc, 1937 cviii, 715-717
- 20 HYLAND, H H Myasthenia gravis results of treatment in 6 cases, Canad Med Assoc Jr, 1936, xxxv, 372-381
- 21 CROSBY, E H Malignant tumors of thymus gland, Am Jr Cancer, 1932, xvi, 461-486
- 22 DOUB, H P Roentgen diagnosis and treatment of thymomata, Radiology, 1930, xiv, 267-281
- 23 VIETS, H R, and SCHWAB, R S Prostigmin in diagnosis of myasthenia gravis, New England J Med, 1935, ccxiii, 1280-1283
- 24 VIETS, H R, and MITCHELL, R S Prostigmin test in myasthenia gravis, New England Jr Med, 1936, ccxv, 1064-1065
- 25 HARVEY, A M, and WHITEHILL, M R Prostigmin as an aid in diagnosis of myasthenia gravis, Jr Am Med Assoc, 1937, cviii, 1329-1333
- 26 KENNEDY, F, and WOLF, A Quinine in myasthenia and prostigmine in myasthenia, clinical evaluation, Jr Am Med Assoc, 1938, cx, 198-202
- 27 LAURENT, L P E Remissions and relapses associated with pregnancy in myasthenia gravis, Lancet, 1931, i, 753-754
- 28 D'AMATO, L Progressive myasthenia gravis, Policlinico, Rome, 1921, xxviii, abstract, Jr Am Med Assoc, 1921, lxxvii, 1848
- 29 EDGEWORTH, H Report of progress on use of ephedrine in case of myasthenia gravis, Jr Am Med Assoc, 1930, xciv, 1136
- 30 BOOTHBY, W M Myasthenia gravis preliminary report on effect of treatment with glycine, Proc. Staff Meet, Mayo Clin, 1932, vii, 557-562
- 31 BOOTHBY, W M Myasthenia gravis effect of treatment with glycine and ephedrine, Proc Staff Meet, Mayo Clin, 1934, ix, 600-603
- 32 MINOT, A S, DODD, K, and RIVEN, S S Use of guanidine hydrochloride in treatment of myasthenia gravis, Jr Am Med Assoc, 1939, cxiii, 553-559
- 33 WALKER, M B Treatment of myasthenia gravis with physostigmine, Lancet, 1934, i, 1200-1201
- 34 DENNY-BROWN, D Physostigmine and belladonna by mouth in myasthenia gravis, Lancet, 1935, i, 767
- 35 WALKER, M B Case showing effect of prostigmin in myasthenia gravis, Proc Roy Soc Med, 1935, xxviii, 759-761
- 36 PRITCHARD, E A B Use of "prostigmin" in treatment of myasthenia gravis, Lancet, 1935, i, 432-434
- 37 LAURENT, L P E Clinical observations on use of prostigmin in treatment of myasthenia gravis, Brit Med Jr, 1935, i, 463-465
- 38 EVERTS, W H Treatment of myasthenia gravis by oral administration of prostigmin, Bull Neurol Inst New York, 1935, iv, 523-530
- 39 LAURENT, L P E, and WALTHER, W W Influence of large doses of potassium chloride on myasthenia gravis, Lancet, 1935, i, 1434-1435
- 40 MINSKI, L, and STOKES, A B Treatment of myasthenia gravis, Brit Med Jr, 1936, i, 1095-1098
- 41 SIMON, H E Myasthenia gravis, effect of treatment with anterior pituitary extract, preliminary report, Jr Am Med Assoc, 1935, civ, 2065-2066
- 42 HSU, Y K, and CH'ENG, Y L Myasthenia gravis with report of case, Chinese Med Jr, 1937, li, 295-314

- 43 HALSTED, W S Results of x-ray treatment of thymus gland in Graves' disease, Bull Johns Hopkins Hosp, 1915, cclxxviii, 55-57
- 44 MELLA, H Irradiation of thymus in myasthenia gravis, Med Clin N Am, 1923, vii, 939-949
- 45 DECKER, H R Primary malignant tumors of thymus gland, with report of two cases, Jr Thoracic Surg, 1935, iv, 445-459
- 46 AYER, J B Myasthenia gravis, New England Jr Med, 1937, ccxvi, 95-96
- 47 RIVEN, S S, and MASON, M F Treatment of myasthenia gravis, South Med Jr, 1937, xxx, 181-190
- 48 THORNER, M W, and YASKIN, J C Treatment of myasthenia gravis, report of 6 cases, Am Jr Med Sci, 1937, cxciiv, 411-418
- 49 GUDERNATSCH, J F in Morris-Jackson human anatomy, 8th Edition, 1925, P Blakiston Son & Co, Philadelphia, page 1319

EDITORIAL

IMMUNITY TO MALARIA

THAT human beings can acquire a considerable degree of resistance to malarial infection has been known for many years. It is a matter of common observation that native inhabitants of tropical regions in which malaria is continuously prevalent—the “hyperendemic” areas—acquire a resistance or at least a tolerance for the infection, so that they show no clinical symptoms of malaria although susceptible newcomers quickly become ill and often succumb to the disease. The conditions under which such immunity develops have been studied with particular care by British observers such as Thomson, Christophers, and James¹. These studies have shown that practically everyone in the community becomes infected in early childhood and is continuously exposed to reinfection. In one such community Wilson² estimated from the prevalence of infected *Anopheles* mosquitoes in the houses that on the average each inmate would receive an infective bite once in twelve days.

The children under two years of age are clinically ill with fever and show enlargement of the spleen and large numbers of parasites in the blood—a condition termed by Christophers the stage of acute infestation. In spite of this these children may show surprisingly little impairment of health if the malaria is not complicated by dietary deficiencies or other forms of parasitism. Possibly some degree of racial immunity may have developed as a result of natural selection during many generations of exposure. In older children parasites are still present but in smaller numbers, and febrile attacks occur only once in two to four weeks—the stage of immune infestation. In adults there may be one or two mild febrile attacks a year, with otherwise no manifestations of illness. Parasites in small numbers can be found in the blood in from 25 to 50 per cent of the cases.

The resistance so acquired is restricted to the species of malaria concerned and largely to the local strains of that species. If such an individual moves into a different region, he may acquire acute malaria from other strains present there. The period of about 15 years elapsing before a newcomer into an infested district secures maximum protection is believed to be the time required for him to acquire and develop an immunity to all the strains of each species occurring in the district.

This resistance is maintained largely by continuous exposure to reinfection. If a native moves into a region free from malaria, he gradually loses his resistance, and on returning to his former home is likely to become

¹ For an excellent review of much of this work see ASHFORD, M. The nature of immunity to malaria in its relationship to antimalarial therapy, *Am Jr Trop Med*, 1936, xvi, 665-678.

² WILSON, D. B. Implications of malarial endemicity in East Africa, *Trans Roy Soc Trop Med and Hyg*, 1938-39, xxxii, 435-446.

acutely ill with the disease. If the frequency of reinfection in such a community is reduced (but not eliminated) by attempts to eradicate mosquitoes, for example, so that the development of active immunity is retarded, there may be an actual increase in the amount of clinical malaria observed. Some therefore question the advisability of undertaking measures of this sort where conditions are such that they can be only partially successful.

This resistance develops fully only if the disease is allowed to run its course without treatment. Quinine or other antimalarial drugs delay and tend to reduce the degree of immunity attained. Furthermore the full effectiveness of quinine depends upon the development of some degree of active immunity by the individual as a response to the infection. The drug temporarily suppresses the clinical manifestations of malaria but by itself does not eradicate the infection. The indiscriminate administration of quinine in such communities in which frequent reinfection can not be prevented may be actually harmful, many believe, by interfering with the development and maintenance of an effective active immunity. Treatment should be restricted, perhaps, to those acutely ill as a symptomatic measure, and not given merely in a vain hope of eradicating the infection.

Experimental work with malaria in birds and monkeys and also in man has, in general, confirmed and amplified the conclusions based on these clinical observations. In the case of avian malaria, it was shown by Wasielewski (1902) that birds which survived the acute attack continued to have a latent infection demonstrable only by the inoculation of blood into normal birds. Such birds can not be reinfected (superinfected) with the same species of parasite as long as the infection persists, although they are susceptible to infection with other species of malaria. A few such birds, however, have succeeded in eradicating the infection completely, and they were then susceptible to reinfection.³

Monkeys also develop a similar type of latent infection during which they resist superinfection with the same strain of parasites.⁴ They show no increase in resistance to other species of malaria, and are usually susceptible to infection with exotic strains of the same species.

The therapeutic use of malaria in the treatment of syphilis has made possible extensive experiments on man. Particularly careful observations have been made by James⁵ in England, and by Boyd⁶ and his associates in this country. In the case of both benign tertian and estivo-autumnal malaria, if the disease is allowed to run its course without treatment, the individual becomes resistant to reinoculation with the same strain of parasite. This

³ MANWELL, R. D. Reciprocal immunity in the avian malarías, *Am Jr Hyg*, 1938, xxvii, 196-211.

⁴ MULLIGAN, H. W., and SINTON, J. A. Studies in immunity in malaria. Superinfection with various strains of monkey malarial parasites, *Rec. Malaria Survey India*, 1933, iii, 529.

⁵ JAMES, S. P. Some general results of study of induced malaria in England, *Trans Roy Soc Trop Med and Hyg*, 1931, xxiv, 477-538.

⁶ BOYD, M. F. On strains or races of the malarial parasites, *Am Jr Trop Med*, 1940, xx, 69-80.

resistance, however, does not extend to other species or to different strains of the same species. The immunity lasts for at least three years. It is still uncertain whether or not the immunity in man depends upon the persistence of some parasites in the body (premunity). It does, however, last long after parasites can no longer be demonstrated by inoculations of 10 c c of blood.

Immunity in malaria thus manifests itself in two ways by a marked diminution in the number of parasites in the blood, and by the ability of the individual, although infected, to live free from sickness under conditions which would cause intense and practically continuous illness in the ordinary individual. There is still considerable doubt, however, as to the mechanism by which this resistance is brought about. The earlier attempts to demonstrate specific antibodies in the serum were for the most part unsuccessful, although Kingsbury (1927) reported obtaining positive complement fixation tests. It was thought that immunity depended mainly upon changes in the tissues, and hyperplasia of reticuloendothelial cells was demonstrated, particularly in the spleen. Furthermore, splenectomy in birds and monkeys in many cases markedly reduces their resistance to malaria and may precipitate an acute fatal attack in an animal harboring a latent infection. It is difficult, however, to explain the remarkable degree of species and strain specificity of the immunity solely on the basis of changes in the tissue cells.

More recently Coggeshall, Eaton and their associates⁷ have demonstrated conclusively the presence of antibodies in the blood of monkeys and human beings with chronic malaria. Their success was largely owing to the use of a more satisfactory antigen prepared from the blood of monkeys heavily infected with *Plasmodium knowlesi*, in which 50 per cent or more of the cells contained parasites. Agglutination, complement fixation and some degree of protective power were demonstrated. Agglutination and protective power were apparently restricted to this species, but complement fixation was less specific in that positive reactions were also obtained with sera from human cases of benign tertian and estivo-autumnal malaria.

It is not likely that these reactions will attain much value as diagnostic procedures. The titer was usually low, the preparation of the antigen difficult and the technic relatively tedious and complicated. The work is interesting, however, in showing that the mechanism of immunity to this protozoan parasite is probably not fundamentally different from that in ordinary bacterial infections.

P W C

⁷ EATON, M. D., and COGGESHALL, L. T. Complement fixation in human malaria with an antigen prepared from the monkey parasite, *Plasmodium knowlesi*, Jr. *Exper. Med.*, 1939, 14, 379-398.

REVIEWS

Manual of Cardiology By WILLIAM DUNCAN REID, A B, M D, F A C P 364 pages, 22 5 × 15 cm Oxford University Press, New York 1940 Price, \$3 50

With a bedside type of presentation, the author furnishes in this volume a personal summary of the important and more recognized aspects of cardiac disease. The book is written chiefly from the standpoint of the student in the nature of a guide to cardiology and is not meant to replace the standard textbooks in which the subject matter and controversial issues are more scientifically treated. Rather it discusses the essentials of diagnosis and treatment of heart disorders in the simplest of terms, with the avowed purpose of aiding the student to apply the textbook material. Only accepted methods having ease of application and bedside usefulness are mentioned, but these are fully evaluated in the light of the author's personal experience.

The book is divided into three parts. Section I deals in an informal conversational manner with the diagnosis, prognosis, treatment and prevention of heart disease. Under diagnosis, the history, physical examination, special examinations and cardiac rhythms are each logically interpreted as to value, important points and means of application. An interesting feature is the use of marginal lines here and there for emphasis and mastery. At the end of the section are appended two charts, one summarizing the data just mentioned, and the other giving the essential characteristics in the differential diagnosis of the common congenital defects.

In Section II, the case histories of 56 patients from the author's files are presented briefly, each with a few questions at the end concerning important points in diagnosis and treatment. Some of the reports are purposely incomplete to stimulate the reader's thought regarding further examinations and details necessary to achieve the diagnosis.

In Section III, the questions raised in Section II are fully discussed and answered for each of the case reports, with arrangements in the same order as in the second section.

In summary, this manual reduces cardiology to its simplest terms for the undergraduate student of medicine, although it should also prove helpful to many general practitioners who feel uncertain regarding their knowledge of cardiac diseases.

R W G

Specialties in Medical Practice Edited by EDGAR VAN NUYS ALLEN, M D Volume I, pages 1-441, Volume II, pages 442-934, 19 5 × 26 cm Thomas Nelson and Sons, New York 1940 Price, \$25 00

The purpose of these volumes is to present to the general practitioner a condensed statement of those parts of each specialty which he can utilize in his practice. The venture is experimental and the final test of whether it has succeeded must be the extent to which general practitioners maintain their subscriptions. It appears to the reviewer that the various authors who have contributed have done their best to present their respective special fields in the manner most useful to the non-specialized readers. The section on ophthalmology seems particularly well done in this respect. However, one may doubt the advisability under the present conditions of practice in this country of the family physician undertaking the operation for chalazion so minutely and interestingly described by the author. In the section on neurology the author has had to contend with the difficulty of condensing too large a subject into too small a space. The result is a section which does not differ greatly from what may be found on the subject of diseases of the nervous system in any of the standard practices of medicine which the general practitioner already possesses. Indeed the discussions of meningitis

and of carbon monoxide poisoning, for example, are far less adequate than those to be found in the usual practice

The section on orthopedic surgery is too condensed to be of great practical value except perhaps as a reminder to one already well acquainted with this field. Obstetrics and gynecology are dealt with at some length and apparently in an adequate and practical manner.

The section on endocrinology should be very valuable to any careful reader. In particular the discussion of the essentials in thyroid surgery should be of interest to those who have not paid previous attention to this matter.

In summary, these volumes are an interesting venture in popularizing the specialties, but not all specialties lend themselves equally well to this form of treatment. It is questionable whether or not the well trained younger practitioner will do better with this system or through a policy of purchasing monographs and standard texts.

M C P

An Introduction to Biochemistry By WILLIAM ROBERT FEARON Second edition
475 pages, 14.5 × 22 cm The C V Mosby Company, St Louis 1940 Price,
\$3.75

The author has "sought to approach the living organism along the less worn path of inorganic biochemistry," since "the microessential constituents of tissues remind us of the fundamental importance of the chemical elements associated with life." Hence the first 62 pages of the book, due to this unusual approach, are devoted to a detailed description of biological elements, inorganic compounds, solutions and colloidal systems. The next 123 pages are devoted to a thorough presentation of carbohydrate, protein and lipid chemistry. This portion of the book is particularly excellent, as are the chapters on biological pigments, enzymes and nutrients (81 pages). The material on digestion and intermediary metabolism (58 pages), although brief, is adequate and contains numerous helpful and instructive diagrams. Then follow chapters on tissue respiration, purines and pyrimidines, nitrogenous bases, urea and other urinary products of excretion (87 pages). A chapter on hormones and a few words on blood and tissue fluids complete the book. An outstanding feature of this text is the ability of the author to write clearly and concisely and to outline and simplify the subject matter. Throughout one is continually impressed by the author's originality especially as to style and as to selection and presentation of material. It should prove to be a satisfactory text for students in general biochemistry.

Absent, however, is the clinical aspect which characterizes the style and subject matter of most of our popular texts on biological chemistry. The author states that he has avoided "some regions of tissue chemistry, especially blood, muscle and nerve, as it is difficult to survey them adequately without physiological and histological assistance outside the scope of this venture." Be that as it may, this reviewer feels that the students and teachers of American medical schools will insist on a text which treats biochemistry more fully from the physiological point of view. Thus they will demand a more adequate treatment of such important subjects as absorption and secretion, urine, blood and muscle chemistry, acid-base regulation, detoxication, animal calorimetry and respiration chemistry. These very important topics are practically ignored in the text under review.

In other respects, however, the book is excellent and should make a welcome addition to our texts on biochemistry. The appearance of the printed page is clear and attractive with the reactions, diagrams and tables well set out. At the conclusion of each chapter is given a list of appropriate reviews and digests pertaining to the subject matter involved. The author has also collected a number of interesting and pertinent quotations from the scientifically minded masters of the past. An introduction has been written for this, the American edition, by Victor C Myers.

E G S

Essentials of Dermatology By NORMAN TOBIAS, M D, Senior Instructor in Dermatology, St Louis University 497 pages, 13 X 20 cm J B Lippincott Co, Philadelphia 1941 Price, \$4.75

This book is a small compend on dermatology, which has been recommended by the author for use by general practitioners and medical students. As the author states in his introduction, the description is concise, and all superfluous writing has been eliminated. There are numerous minor errors in the early part of the text, especially regarding the various biologic tests used in dermatology. These errors may prove confusing to students. The pictures are good, and are arranged in their proper position in the text. There is also a good chapter on syphilis and the treatment of syphilis, which follows the principles of the cooperative clinical group.

Collectively, this book is somewhat better than the average small text in dermatology, but it has no distinctive features.

H M R, JR

COLLEGE NEWS NOTES

NEW LIFE MEMBER

Dr Walter J Wilson, Sr, F A C P, Detroit, Mich, became a Life Member of the American College of Physicians on June 16, 1941

GIFTS TO THE COLLEGE LIBRARY

Book

Dr Samuel A Levine, F A C P, Boston, Mass—"Medical Papers" (Bound collection of reprints)

Reprints

Dr Otis L Anderson, F A C P, Chicago, Ill—2 reprints,
Dr Irving L Applebaum (Associate), Newark, N J—6 reprints,
Dr J Edward Berk (Associate), Philadelphia, Pa—3 reprints,
Dr Edward G Billings, F A C P, Denver, Colo—1 reprint,
Dr Albert G Bower, F A C P, Glendale, Calif—1 reprint,
Dr Julius H Comroe, Jr (Associate), Philadelphia, Pa—1 reprint,
Dr Orin J Farness (Associate), Tucson, Ariz—2 reprints,
Dr James M Flynn, F A C P, Rochester, N Y—2 reprints,
Dr Hyman I Goldstein (Associate), Camden, N J—1 reprint,
Dr Barnett Greenhouse, F A C P, New Haven, Conn—2 reprints,
Dr Harold J Harris (Associate), Brooklyn, N Y—1 reprint,
Dr Meredith B Hesdorffer (Associate), Missoula, Mont—1 reprint,
Dr Egon E Kattwinkel, F A C P, West Newton, Mass—1 reprint,
Dr Moise D Levy, F A C P, Houston, Tex—3 reprints,
Dr Victor W Logan, F A C P, New York, N Y—1 reprint,
Dr Sydney R Miller, F A C P, Baltimore, Md—3 reprints,
Dr Frederick W Mulsow, F A C P, Cedar Rapids, Iowa—1 reprint,
Dr Robert J Needles, F A C P, St Petersburg, Fla—3 reprints,
Dr Abe Ravin (Associate), Denver, Colo—1 reprint,
Dr Nathaniel E Reich (Associate), Brooklyn, N Y—4 reprints,
Dr David R Sacks, F A C P, San Antonio, Tex—1 reprint,
Dr David J Sandweiss, F A C P, Detroit, Mich—2 reprints,
Dr Charles H Sprague, F A C P, Boise, Idaho—2 reprints,
Dr Aaron A Sprong (Associate), Sterling, Kan—3 reprints,
Dr Robert T Sutherland, F A C P, Oakland, Calif—1 reprint,
Dr Harold Swanberg, F A C P, Quincy, Ill—4 reprints,
Dr John W Wilce, F A C P, Columbus, Ohio—1 reprint,
Dr Zolton T Witschaffter (Associate), Cleveland, Ohio—4 reprints

The Board of Trustees of the American Medical Association has announced the appointment of Dr Theodore G Klumpp, F A C P, Washington, D C, as Secretary of the Council on Pharmacy and Chemistry of the Association. Dr Klumpp will take office on July 1, 1941. Dr Klumpp will also serve as Director of the Chemical Laboratory and Director of the Division of Foods, Drugs and Physical Therapy of the Association.

The decoration of the White Cravat with Red and Blue Borders of the Illustrious Order of the Jade was granted to Dr Jacob C Geiger, F A C P , San Francisco, Calif , by Generalissimo Chiang Kai-shek of China, on the 29th anniversary of the National Revolution, October 10, 1940 This award bore the following citation

"For work of merit in public health in the Republic of China and among the Chinese population in San Francisco"

On May 2, 1941, Dr Rufus S Reeves, F A C P , Philadelphia, Pa , received the 18th annual Strittmatter Award The award consists of a gold medal and a scroll and was founded by the late Dr I P Strittmatter for donation to the physician who makes the most valuable contribution of the year in Philadelphia to the healing arts This award was given Dr Reeves in recognition of his work as Chairman of the Annual Postgraduate Institute of the Philadelphia County Medical Society

Dr Ella Roberts (Associate), Philadelphia, Pa , has been appointed Medical Director of the Children's Heart Hospital, Philadelphia, Pa , to succeed Dr Oswald F Hedley, F A C P , who has been transferred to the National Health Institute, Bethesda, Md

At the 42nd Annual Meeting of the American Therapeutic Society held in Cleveland, Ohio, May 30-31, 1941, Dr Louis Faugeres Bishop, Jr , F A C P , New York, N Y , retiring President, was elected a member of the Council for the succeeding five years

Dr Samuel M Feinberg, F A C P , Chicago, Ill , was elected President-Elect of the American Association for the Study of Allergy at the 19th Annual Meeting of the Association held in Cleveland, Ohio, June 2, 1941

Dr Harold G Trimble, F A C P , Oakland, has been elected President of the California Tuberculosis Association and Dr E Richmond Ware, F A C P , Los Angeles, Vice-President Among the Directors of the Association are Drs Chesley Bush, F A C P , Livermore, Carl R Howson, F A C P , Los Angeles, Philip H Pierson, F A C P , San Francisco, Sidney J Shipman, F A C P , San Francisco, Rudolph H Sundberg, F A C P , San Diego, and William C Voorsanger, F A C P , San Francisco

On May 21, 1941, Dr Sigmund S Greenbaum, F A C P , Philadelphia, Pa , addressed the Medico-Dental Society of Atlantic City, N J , on "Diseases of the Mouth"

The Society for Investigative Dermatology, Inc , held its 4th Annual Meeting in Cleveland, Ohio, June 3, 1941 The Presidential Address was given by Dr J Bedford Shelmire, F A C P , Dallas, Tex The title of his address was "Study of Sensitivity to Poison Ivy"

Dr Ralph Pemberton, F A C P , Philadelphia, Pa , spoke on "The Present Status and Treatment of Chronic Arthritis" at the meeting of the Oklahoma State Medical Association in Oklahoma City, May 20, 1941

Dr John J Weber (Associate), Brooklyn, N Y., has been appointed Active Consulting Physician to the Kingston Avenue Hospital, Brooklyn

On May 6, 1941, Dr Hyman I Goldstein (Associate), Camden, N J, addressed the 17th Annual Meeting of the American Association of the History of Medicine, held in Atlantic City, N J, on "The History of Ulcer of the Stomach and the Duodenum"

The State Committee of the New Jersey Gastro-enterological Society for the 7th Annual Convention of the National Gastroenterological Association, to be held in Atlantic City, N J, during the spring of 1942, includes Dr Hyman I Goldstein (Associate), Camden, Chairman, Dr Manfred Kraemer, F A C P, Newark, Vice-Chairman and Secretary, Dr Louis L Peikel, F A C P, Jersey City, and Dr Sigurd W Johnsen, F A C P, Passaic

Dr William Dameshek, F A C P, Boston, Mass, spoke on "The Spleen Facts and Fancies" at the 89th Annual Session of the Maine Medical Association, held in York Harbor, June 22-24, 1941

Among the speakers at the annual Conference of Health Officers and Public Health Nurses, held in Saratoga Springs, N Y, June 24-26, 1941, were

Dr Soma Weiss, F A C P, Boston, Mass—"Heart Disease",

Dr Russell M Wilder, F A C P, Rochester, Minn—"Nutrition—A Public Health Problem",

Dr Lawrence Kolb, F A C P, Washington, D C—"Alcoholism and Public Health"

Among the speakers at the recent annual meeting of the Medical Society of the State of North Carolina, in Pinehurst, N C, were

Dr Louis H Clerf, F A C P, Philadelphia, Pa—"Tumors of the Larynx and Hypopharynx",

Dr Wilburt C Davison, F A C P, Durham, N C—"The First Ten Years of Duke University School of Medicine and Duke Hospital",

Dr William T Rainey, F A C P, Fayetteville, N C—"The Management of Congestive Heart Failure"

The Committee on Nutrition and Deficiency Diseases of the Philadelphia County Medical Society and the Philadelphia Child Health Society recently sponsored a special meeting on nutrition. Dr Rufus S Reeves, F A C P, Philadelphia, Pa, spoke on "Nutrition—The Cornerstone of National Defense," and Dr Herbert T Kelly, F A C P, Philadelphia, Pa, spoke on "Medical Aspects of Nutrition"

The Pacific Northwest Medical Association held its 18th Annual Meeting in Spokane, Wash, June 25-28, 1941. Among the speakers at this meeting were

Dr Russell L Cecil, F A C P, New York, N Y—"Diagnosis and Treatment of Infectious Arthritis, of Osteoarthritis and of Gouty Arthritis",

Dr Louis H Clerf, F A C P, Philadelphia, Pa—"Clinical Significance of Hoarseness and Its Importance in Cancer of the Larynx", "Bronchoscopy in Non-tuberculous Pulmonary Disease", "The Esophagus and Its Diseases",

Dr. William J Kerr, F A C P, San Francisco, Calif—"Clinical Use of the Symballophone, Pathologic and Physiologic Factors in Coronary Occlusion, Treatment of Angina Pectoris"

Dr James K Hall (Associate), Richmond, Va, was installed as President of the American Psychiatric Association at its recent annual meeting in Richmond, Va

Dr Rufus S Reeves, F A C P, Philadelphia, Pa, spoke on "Nutrition and National Defense" at a meeting of the Ex-Residents and Fellows of the Robert Packer Hospital in Sayre, Pa, June 20, 1941

Dr Abraham M Rabiner (Associate), Brooklyn, N Y, has been appointed Clinical Director of the Jewish Sanitarium and Hospital for Chronic Diseases, Brooklyn, N Y

Dr Archibald A Barron, F A C P, Charlotte, was elected President of the North Carolina Neuropsychiatric Association, and Dr Fonso B Watkins, F A C P, Morganton, Vice-President, at the recent meeting of this society

The Utah State Medical Association held its 47th Annual Meeting June 12-14, 1941, in Salt Lake City Among the guest speakers at this meeting were

Dr Edward H Rynearson, F A C P, Rochester, Minn—"Hyperinsulinism", "Endocrinology—A Critical Review",

Dr Cyrus C Sturgis, F A C P, Ann Arbor, Mich—"Treatment of the Anemias", "The Hemorrhagic Diseases"

The American Neurological Association held its 67th Annual Meeting in Atlantic City, N J, June 9-11, 1941 Dr Norman Jolliffe, F A C P, New York, N Y, spoke on "Clinical and Chemical Studies in Wernicke's Syndrome", and Dr Lawrence Kolb, F A C P, Washington, D C, spoke on "Degeneration of the Primary Sensory Neuron in Pigs from Nutritional Deficiency"

The Dallas Southern Clinical Society has launched a program of courses for the continuation of medical study Present plans of the Society are to hold these courses during June, October, and January The first group of courses was conducted June 23-25, 1941, and the following subjects offered Medicine—Cardiology, Surgery—Fractures, Obstetrics—Normal and Abnormal Labor, Pediatrics—Nutrition and Gastrointestinal Diseases The courses will be conducted in the hospitals and clinics of Dallas The Society has made an effort to limit the subjects to one particular phase of the specialty and to cover that subject thoroughly Among those who participated in the first group of courses were

Dr Henry M Winans, F A C P—"Hemodynamics of the Circulation" and "Diagnosis and Treatment of Cardiac Arrhythmias",

Dr J Shirley Sweeney, F A C P—"Reasons for Accepted Classification and Recommended Terminology in Heart Disease",

Dr W Grady Reddick, F A C P—"Roentgen Aid in the Diagnosis of Heart Disease" and "Demonstration of Bed Patients with Various Types of Heart Disease Differential Diagnosis, Treatment, Prognosis and Discussion",

Dr William H Potts, F A C P—"Circulatory Function Tests",

Dr Robert M Barton, F A C P , and Dr Merritt B Whitten (Associate)—
 “Principals and Practical Application of Electrocardiography”,

Dr David W Carter, J1 , F A C P —“Heart Failure Edema, Dyspnea, Cyanosis”
 and “The Treatment of Cardiac Failure”,

Dr Samuel A Shelburne, F A C P —“Cardiac Clinic Demonstration of Ambulatory Heart Patients Differential Diagnosis, Treatment, Prognosis and Discussion”,

Dr William H Bradford (Associate)—“General Food Requirements in Infancy Normal, Twins, Premature, Diabetic”,

Dr John G Young, F A C P —“Breast Feeding,” “Formula Feeding” and
 “Use and Abuse of Laxatives and Cathartics”,

Dr John E Ashby (Associate)—“Oral Disorders and Dentition”,

Dr H Leslie Moore, F A C P —“Differential Diagnosis of Appendicitis”

Herbert T Kelly, M D , F A C P , Philadelphia, Pa , participated in a symposium on the “Management of Various Types of Obesity” presented at the Spring Clinic of the Ingham County Medical Society at Lansing, Michigan, May 1, 1941

At the annual meeting of the Pennsylvania State Dietetic Association at Philadelphia, May 22, 1941, Dr Kelly presented a paper on “The Nutrition Program of the Medical Society of the State of Pennsylvania” He also addressed the 73rd annual convention of the Pennsylvania State Dental Society at Bedford, Pa , on June 3, 1941 on “Medical Aspects of Dentistry”, and on June 6, 1941, he addressed the Columbia County Medical Society at Bloomsburg, Pa , on “Nutritional Management of the Pre- and Postoperative Patients”

Dr Carl J Wiggers, F A C P , professor of physiology in the School of Medicine of Western Reserve University, was awarded the honorary degree of Doctor of Science by the University of Michigan at its commencement exercises, June 21

An authority on the physiology of the heart and circulation, in recent years Dr Wiggers has concentrated upon phases of research in his subject, including ventricular fibrillation, the disturbance which stops the heart in acute and chronic heart diseases, in angina pectoris and coronary occlusion and in accidental electrocution, and has also conducted studies of extra-cardiac factors of circulation, the part the blood vessels play in the blood flow particularly in failure of the circulation in surgical shock and similar conditions For this research he has had appropriations from the John and Mary R Markle Foundation of New York and the Commonwealth Fund of New York

Dr Wiggers graduated from the University of Michigan Medical School in 1906, and taught there and at Cornell and in the University Medical College of New York City before joining the faculty of Western Reserve University in 1918

MARYLAND MEMBERS HOLD REGIONAL SPRING MEETING

The Spring meeting of the Maryland Chapter of the American College of Physicians was held at a dinner in Baltimore, May 28, 1941 There were sixty-two members present As has been customary at the Spring meetings the major topic of discussion was the recent Annual Session of the College Dr Wetherbee Fort, President of the Maryland Chapter and other members who attended the Boston meeting wished to express their appreciation to the College for the delightful musical evening in Symphony Hall

Dr John T King was elected President for the coming year

Under the chairmanship of Dr Walter L Biering, F A C P , Iowa State Health Commissioner, Des Moines, the Iowa State Department of Health and the Iowa State Medical Society sponsored a Special Institute on Industrial Health from June 23 to 27, with a day each in Burlington, Cedar Rapids, Mason City, Sioux City and Des Moines. Dr Lee R Woodward, F A C P , was in charge of local arrangements at Mason City. The same subjects were covered at each center or city—"The Industrial Back," "Industrial Hygiene Control Measures," "Management of Multiple Injuries," "Demonstration of Methods Employed in Industrial Hygiene," "Medical Control Measures in Industry," "Medical Relationships in Compensation" and "Medicine in Industry."

Charles W Clarke, M A , M D , F A C P , Executive Director, the American Social Hygiene Association, has been appointed lecturer in the School of Public Health, Harvard University, and Visiting Professor in the School of Tropical Medicine, University of Puerto Rico.

Dr J W Torbett, Sr, F A C P spoke on "Some Profound Cases of Malnutrition Treated Successfully with Insulin" at a recent meeting of the 12th District Medical Society in Waco, Texas.

Dr Joseph H Batach addressed the Albany Medical College, Albany, N Y on May 29, 1941. His topic was "Inheritance and Tumors." The evening of that same day he addressed The Academy of Medicine of Glens Falls, N Y on the subject "Present Day Treatment of Diabetes and Its Complications."

Dr J C Zillhardt (Associate), Binghamton, N Y was guest speaker at the Tioga County Medical Society meeting held in Owego, N Y on June 3, 1941. Dr Zillhardt spoke on "Blood Transfusion and Blood Banks."

The American Gastro-Enterological Association has elected new officers as follows: Dr Russell S Boles, F A C P , President, Dr Sara M Jordan, F A C P , First Vice-President, Dr A H Aaron, F A C P , Second Vice-President, Dr J G Mateer, F A C P , Treasurer, and Dr Julian M Ruffin, F A C P , Recorder.

The American Foundation for Tropical Medicine, Inc announces the establishment of a limited number of Fellowships for the post graduate course in Tropical Medicine at The Tulane University of Louisiana. The course is given for a period of four and one half months, beginning in September of each year. A certificate will be awarded to physicians who successfully complete the course. These Fellowships are available for young, duly qualified physicians who are citizens of the Republics of Mexico, Central and South America.

In addition to the tuition fee which will be met by the Foundation, each Fellowship will furnish \$700 for travel and maintenance.

Applicants for the Fellowships in Tropical Medicine of the American Foundation for Tropical Medicine, Inc, should apply to the Director of The Department of Graduate Medicine, School of Medicine, The Tulane University of Louisiana, 1430 Tulane Avenue, New Orleans, La, U S A. Completed application forms will be submitted to the Council of the American Academy of Tropical Medicine, who will award the Fellowships.

In view of the national defense requirements Mr. Harvey S Firestone, Jr has advocated the saving of all used rubber in this country Mr Firestone makes the following valuable suggestions about the disposition of used hospital rubber

"It would be my suggestion that you sell your hospital's scrap rubber, including that from sheeting, hot water bottles, rubber gloves, tubing, etc, to any scrap dealer who will give you the best price for it In that way it will find a route to the reclaiming plants and the hospital will obtain some salvage value from it Market prices of scrap rubber fluctuate the same as do prices of any other commodities Further, different prices for the same grades will prevail in different communities because of differences in shipping costs that must be incurred to get the rubber to points where it can be reclaimed Speaking generally, however, the types of scrap rubber which a hospital can accumulate will vary in price from less than a cent a pound to several cents per pound, with gloves and other 'pure gum' articles commanding the higher prices If the scrap is sorted by articles or grades of rubber, it should bring more than if sold in one bulk lot "

The Medical and Surgical Relief Committee, a nationwide organization consisting of some 300 physicians and surgeons throughout the country who collect surplus medical supplies and, when necessary, funds for the relief of civilians and armed forces in Great Britain and allied countries, have undertaken the sale of an emblem The emblem is a lapel ornament in the form of a modified Caduceus combined with a sword of mercy and sells for \$1 00 The headquarters of this Committee are located at 420 Lexington Ave, New York, N Y

Correction May 1941 ANNALS, page 2147, the dates should read as follows first paragraph, July 9, 1925, fourth paragraph, line 1, December 1923, line 5, January 20, 1925

OBITUARIES

DR WILLIAM HENRY WALSH

Carving for himself a unique career, after early service in the Medical Department of the United States Army and with the United States Public Health Service, Dr William Henry Walsh brought honor to himself and to the profession of which he was a member by devoting much of his life to the betterment of hospitals. Scores of communities in the United States, Canada, and other countries are benefiting today from hospital service planned to meet their special needs with the advice and under the direction of Dr Walsh. His fame as a consultant on hospital planning, equipment, organization and management spread to other nations, and for more than two decades he was recognized as a leading world authority on hospitals.

At a time when a few of our younger physicians may be deploring the interruption of their careers incident to military service, it is of interest to note that it was in the Army that this great medical career began. In 1898, at the age of 16, after graduation from Girard College, Philadelphia, he enlisted and served in the Medical Department of the United States Army in hospitals in Washington, Virginia and New Mexico, and in regimental duty in the Philippine Islands. That he became immediately an enthusiastic fighter in the war on disease is proved by the fact that before he was 20 years old, he was made chief sanitary inspector for the Insular Bureau of Health, and served in Manila for two years during a cholera epidemic.

Desire to be better prepared for the work which attracted him, led to enrollment in 1904 in the Medico Chirurgical College of Philadelphia and to his graduation from that school in 1909. Internship in the U S Marine Hospital in Baltimore and a year in the Immigration Service in Philadelphia followed. In 1911 Dr Walsh was appointed Medical Director of the Philadelphia Hospital for Contagious Diseases. While serving in this capacity, he gave his first major talk at a conference of the American Hospital Association in 1914, on the subject, "The Hospital Superintendent—Past, Present, and Future." Published in the January, 1915, issue of *Modern Hospital*, as well as in the Transactions of the Association, it is the first of a long series of articles on hospital subjects credited to his pen.

In 1914 Dr Walsh was appointed Chief Resident Physician at the Philadelphia General Hospital, the following year he became Medical Director of the Childrens Hospital in the same city. In 1915 he was attracted to hospital association work, becoming the first Executive Secretary of the American Hospital Association. He held that position until 1917 when he was assigned to duty in command of Base Hospital No. 58 at Camp Grant which he organized and took to France in August, 1918, serving successively as Capt. Major and Lt. Colonel. Returning to America after the war, he was appointed Secretary of the Hospital Board of the U S Public Health Serv-

ice, and was later in command of the Public Health Service Hospital for Tuberculosis at Markleton, Pennsylvania. In 1924 we find Lieutenant-Colonel Walsh receiving a letter of commendation from Consul George P. Waller of the American Consular Service for the "constructive executive and diplomatic ability" shown in "guiding and directing the Vicente d'Antoni Memorial Hospital at La Ceiba, Honduras, from its conception throughout its embryonic period in the brain of yourself, your architects and builders, up to the point where you delivered it on February 3, 1924, a living, functioning entity—the finest and best equipped hospital between New Orleans and Panama"—and also for care and treatment of wounded Americans and natives during the revolution in Honduras.

In 1924 Dr. Walsh resumed the secretaryship of the American Hospital Association, while pursuing part time hospital consultation service. Rapidly the demand for this special service grew, until in 1928 he was obliged to resign in order to give full time to it. In the years between 1928 and 1941, testimonial after testimonial was written expressing appreciation of his help in the planning, building, organizing and management of hospitals.

His purposeful career has ended by death, March 28, 1941. It was colorful and varied, and brought him friendships and influence in high places over a wide territory. Everywhere, by his earnestness and trustworthiness, he won the kind of response from which grew impetus to greater efficiency, better service, more regard for the needs of the hospital patient.

The hospitals that he served directly through his special services, and the hospitals that were influenced less directly through his work on committees of the American Hospital Association, his talks at hospital conferences, and his numerous articles on hospital subjects, all reflect evidence of his ambition for improved practices and policy. He stimulated the entire hospital field. There will be no end to his influence. The service that he founded and the legacy that he left will endure. His personal, thoughtful, kindly counsel will be missed by many of us who sought it frequently, but his example of the high type of physician who is also an able administrator and a skilled organizer will live for many others to emulate. His was truly a career of practical service that has helped to create the Modern Hospital.

MALCOLM T. MACEachern, M.D., F.A.C.P.,

Chicago, Ill.

DR. EDWARD WEST HOLLINGSWORTH

Dr. Edward West Hollingsworth, F.A.C.P., Oak Park, Ill., was born on April 26, 1893, in Bel Air, Maryland, the son of Roberta Y. and the late Dr. Charles A. Hollingsworth. After receiving his pre-medical education at Swarthmore College, he graduated with the degree of Doctor of Medicine from the Medical School of the University of Virginia in 1918.

He served in the Medical Enlisted Reserve Corps of the Army from January 1918 to April 1919.

Following internship at the Lenox Hill Hospital, New York City, Dr Hollingsworth was commissioned as Assistant Surgeon (R) in the U S Public Health Service on January 23, 1920. He served with the U S Public Health Service Hospital No 45, Biltmore, North Carolina until September 1921, at which time he was transferred to the Veterans Administration Facility, Hines, Illinois. He served continuously at the Hines Hospital in various capacities since that date and was recently Chief of the General Medical Service.

Dr Hollingsworth specialized for a number of years in cardiology. He avidly sought after the truth in medicine and was vitally interested in the correlation of pathological material and its clinical manifestations. His opinions were respected by all members of the medical staff and his kindly approach to patients likewise endeared him to them.

Dr Hollingsworth took an active interest in civic and medical matters. He was a Fellow of the American College of Physicians, the American Medical Association, a member of the Chicago Medical Society, American Heart Association, Chicago Heart Association and of the Central Society for Clinical Research. He was also a member of the Phi Gamma Delta Fraternity, a member of the Contract Bridge Club of Chicago, life member of the Chicago Art Institute, member of the University of Virginia Alumni Association of Chicago, of Swarthmore University Alumni Association of Chicago and a member of the Christ Episcopal Church of River Forest, Illinois. He was a supporter of and contributor to many community and welfare organizations in Oak Park and River Forest.

Dr Hollingsworth's death from coronary thrombosis came suddenly and unexpectedly, March 15, 1941. He was honored and respected not only by the staff of the Hines Hospital, but also by the members of the profession in his community and in Chicago.

He is survived by his widow, a daughter, Irene, mother, Mrs Roberta Y Hollingsworth, two brothers, Dr William Y Hollingsworth, Commanding Officer at the Marine Hospital, Staten Island, N Y, and Karl A Hollingsworth of Sanysidro, California, and a sister, Dr Roberta Y Hollingsworth, Dean of Women at The University of Virginia.

H F MACHLAN, M D, F A C P,
Chief Medical Officer, Veterans Administration, Hines, Ill

DR LEON THAYER STEM

Dr L T Stem was born in Rover, Tennessee, in 1884. He attended the University of Tennessee College of Medicine from which he was graduated with high honors in 1909. The next two years were spent in postgraduate study, after which he entered general medical practice. Throughout his life he frequently did postgraduate work, some of which was at New York Postgraduate Medical School and some at Presbyterian Hospital, New York City. He also took a clinical European tour in 1926. During the world war he

was stationed at the Army Medical School and for some time was Staff Physician at U S Army General Hospital No 19, Oteen, N C After his return to Chattanooga he was Chief of Staff at Pine Breeze Sanitarium for several years, and was Internist on the Staff at Baroness Erlanger Hospital, Chattanooga, until the time of his retirement He was President of the Chattanooga and Hamilton County Medical Society in 1925 and President of the Tennessee State Medical Society in 1929-30 He was a member of the Southern Medical Society and American Medical Association, and was elected a Fellow of the American College of Physicians in 1923

In 1934 Dr Stem was forced to retire from active practice, because of arthritis and heart disease, at which time he moved to Sarasota, Florida, in an attempt to regain his health In 1938 he developed a left sided hemiplegia and from then his condition gradually became worse and death occurred May 15, 1941, as a result of congestive heart failure

It has often been said of physicians that they gave their lives for their patients, and in the case of Dr Stem this was undoubtedly true, for he continued with his work long after he had been warned by his physicians that to do so meant irreparable damage to his health, and this in face of the fact that there was no financial necessity for him to make this sacrifice

Until he was forced to retire, he never refused to see a patient, regardless of whether it was day or night, whether the weather was good or bad, or whether the patient was pay or charity He had an enormous practice and his patients loved him blindly and trusted him implicitly They depended on him for advice on all subjects He was exceedingly kind and very tolerant of human frailties, but he did not have any patience with those who failed to live up to their word or deliberately misled him

He was a devoted father and kind thoughtful husband One of his four sons is a doctor and another is still in medical school He has one brother who is also a doctor Next to his devotion to his profession and almost equal to that for his family, his loyalty to organized medicine stands out as one of his dominant interests The many positions which he held in various organizations were given in reward for years of unfailing interest and untiring service

He was always helpful to younger physicians and his life was an inspiration to them as well as to all of his associates He was a devoted friend and a considerate, courteous and wise consultant His loss will be keenly felt

CHARLES R THOMAS, M D , F A C P ,
Chattanooga, Tenn

DR WILLIAM FITCH CHENEY

Dr William Fitch Cheney, F A C P , San Francisco, California, died on April 10, 1941 Born at Canandaigua, N Y in 1866, he received his B L at the University of California in 1885, followed by the degree of M D

from the former Cooper Medical College, now Stanford University Medical School. He served as Professor of Principles and Practice of Medicine at Cooper Medical College from 1898 to 1909, Clinical Professor of Medicine, Stanford University Medical School from 1909 to 1932, when he was made Clinical Professor of Medicine, Emeritus, which position he held up to the time of his death.

He was a member of the San Francisco County Medical Society, serving as President in 1905, a member of the California State Medical Association, the American Medical Association, the American Gastro-enterological Association, the American Therapeutic Society, a Diplomate of the American Board of Internal Medicine, Fellow of the American College of Physicians since February 24, 1926.

Dr. Cheney was one of the first and better known gastro-enterologists of the Pacific Coast and gained a national reputation in this field. A dignified and gentlemanly figure, he commanded the respect and admiration of his fellow physicians. He represented only the charming types of physician, who combined with professional attainments a background of culture and wide range of interests.

His heritage of intellectual attainment was passed on to his son, Dr. Garnett Cheney of San Francisco, and to the many students and interns who came in contact with him during the many years of his teaching career.

ERNEST H. FALCONER, M.D.,
Governor for Northern California

DR. JOHN DUDLEY DUNHAM

Dr. John Dudley Dunham (F.A.C.P.), Columbus, Ohio, died January 28, 1941, of coronary occlusion, aged 67 years.

Dr. Dunham received his A.B. degree at the University of Michigan in 1894 and his M.D. degree at the Ohio Medical University in 1897. His postgraduate work was done at Columbia University in New York City and at the University of Berlin.

Dr. Dunham's great interest in the medical profession is manifested by the following activities: Instructor of Bacteriology, Ohio Medical University, 1898-1900; Director of Columbus City Board of Health Laboratory, 1898-1901; Professor of Medicine, Starling Medical College, 1901-1914; Professor of Medicine, College of Medicine, Ohio State University, 1924-1929. He was a member of the medical staffs of Mt. Carmel, White Cross, and Grant Hospitals.

He was a member of the Columbus Academy of Medicine, serving as its President in 1914. He was also a member of the Ohio State Medical Association and the American Medical Association in which he had served as chairman of the Medical Section. He was a member of the American Society of Gastro-Enterology. In 1924 Dr. Dunham was made a Fellow of

the American College of Physicians and served as a Governor for the College for the State of Ohio from 1925 to 1931

He was Major of the Medical Corps, U S A , from May 1918 to April 1919 and as such was chief of the Medical Service at General Hospital No 12, Biltmore, North Carolina, and later of the United States Military Academy, West Point At the time of his death he was a Lieutenant-Colonel of the Medical Officers Reserve Corps

He was a member of the Phi Delta Theta Fraternity and an active member of the American Legion

Dr Dunham was the first physician in Central Ohio to strictly limit his practice to Internal Medicine, which he did in 1901 He was held in high esteem by his colleagues

He is survived by his widow, two daughters, and two sons

CHARLES W MCGAVRAN, M D , F A C P ,
Columbus, Ohio

ANNALS OF INTERNAL MEDICINE

VOLUME 15

AUGUST, 1941

NUMBER 2

INDUSTRIAL HYGIENE IN THE NATIONAL DEFENSE PROGRAM *

By J J BLOOMFIELD, Sanitary Engineer, U S Public Health Service,
Washington, D C

TODAY it is acknowledged that military mobilization and expansion are impossible without industrial mobilization and expansion. We know that steps to perfect the Nation's industrial mobilization are being taken every day, and that any condition which tends to retard efficient production of defense materials is considered of major importance.

We know that the industrial expansion *now* in progress brings in its wake numerous health problems affecting the working population. Do these health problems have any significant effect on the *rate* and *quality* of our industrial production? If so, what provisions are being made today to solve these problems?

EFFECT OF INDUSTRIAL DISABILITY ON PRODUCTION

Although, today, we know how to control the majority of industrial health hazards, the application of that knowledge lags far behind, so that even in normal times, a large proportion of our industrial workers are confronted with working conditions unfavorable to health and well-being. *Even in normal periods*, the loss of time due to all types of disability in industry amounts to the staggering total of 350,000,000 days a year, or considerably more than 1,000,000 work years a year. This burden confronts the defense program and must be reckoned with in any production schedule. It is realized that these astronomical figures are difficult to grasp. The *monetary* cost alone of this lost time amounts to the overwhelming sum of approximately ten billions of dollars. Compare this with the national debt!

However, if we do not wish to consider these figures in terms of money, nor even in terms of health and welfare, we can at *least* consider them in

* Read at the Boston meeting of the American College of Physicians, Twenty-fifth Annual Session, April 24, 1941

terms of what they mean to our present defense program. Estimates made by the U S Bureau of Labor Statistics are available, which show the number of man-hours necessary to produce certain materials vital to defense. The 350,000,000 days lost due to disability among workers, if interpreted in defense materials, are the number of days it takes to build 52 battleships, 164,706 combat tanks, or 107 average size cantonments. If by applying our present knowledge of industrial hygiene to such an extent that we could show a 10 per cent reduction in these time losses, and 10 per cent is a very modest objective, it is evident that we would have done much to eliminate one bottleneck in the defense program which merits serious consideration.

There is yet another factor which must be realized in any discussion of the relationship between industrial health and the national defense program. If we do not today take steps to create safe and healthful working conditions for the workers employed in our defense industries, then we may anticipate that, after the emergency is over, there will be thousands of men and women whose health has been irreparably damaged because of exposure to harmful conditions in those industries. The socio-economic implications of this fact also merit serious consideration.

What then are the specific industrial health problems which we must solve, if we would avoid delay in the defense program and impaired national health after the emergency?

THE PROBLEM IN NORMAL TIMES

Despite years of continued improvement in industrial hygiene, industrial accidents in the United States still cause 17,000 deaths, 75,000 permanent, and 1,400,000 temporary disabilities annually. Recent surveys of industrial plants throughout the Nation show that more than 1,000,000 persons are engaged in work where industrial dusts can create a serious health hazard under certain conditions, nearly 1,000,000 persons are handling lead and its compounds, and another 50,000 are using mercury and its compounds. In addition, many millions of workers are exposed to materials which may produce disabling skin diseases.

Of greatest significance, however, is the enormous waste of life and efficiency resulting from nonindustrial illness among workers. As a matter of fact, the amount of time lost from work, because of ordinary illnesses, is 15 times as great as the total time lost due to accidents and occupational diseases combined. It has also been demonstrated that industrial workers have a higher rate of physical defects than do nonindustrial workers, and that excessive mortality is especially notable among unskilled employees, whose death rate from all causes is 100 per cent or more in excess of the rate among agricultural workers.

These, then, are some of the problems of industrial hygiene confronting our nation in *normal* times.

THE PROBLEM IN DEFENSE

Needless to say, industrial mobilization in recent months has greatly augmented industrial health problems. Able-bodied men are being drawn into military service and are being replaced in industry by women, young adults, and older men. Many of these new workers are not as physically fit as the men they replace, and many of them, especially women, are unaccustomed to an industrial environment. *Unless* that environment is made safe for these new industrial recruits, and *unless* these workers are made health and safety conscious, we may expect a marked rise in accident and disease rates.

The problem of fatigue, so important in the first World War, will again appear as a result of the speed-up in industrial production. Hazardous chemicals will be used with little or no time to determine in advance their toxic nature. We may expect crowding in many factories, and under the pressure of the emergency, we may expect a tendency to relax that eternal vigilance, so necessary for the prevention of accidents and diseases among workers. Dr. Parran has stated that our industrial machines are rated as the most efficient in the world, and he rightfully insists that the men and women who operate these machines should be given the opportunity to do so with a comparable efficiency.

These, in brief, are some of the industrial health problems facing us today. Have we the organization and the program for solving these problems?

ORGANIZATION AND PROGRAM

Fortunately, the groundwork laid by research during the past quarter century, and the organization developed during the past several years for the application of this research by industry and by the States, finds us better prepared to cope with industrial health problems than at any other time in our industrial history. It is universally conceded that the prevention of conditions inimical to health is *always* cheaper and *more* effective than attempts to correct them after they have gained headway. We know that *every* job *can* be done *safely* by applying our present knowledge of industrial hygiene.

Ordinarily, the legal responsibility for protecting the health of our workers is a function of official local public health agencies. In view of the fact, however, that industrial expansion for defense purposes has been instigated by the federal government, the communities where such expansion arises may reasonably expect the federal government to assist them in accomplishing the task of protecting and improving the health and efficiency of the workers in defense industries. Only by so doing may we assure ourselves of an uninterrupted flow of materials so vital for the defense program.

The Organization. The organization which has been effected to achieve this objective may be described as follows. The Health and Medical Committee of the Federal Security Agency, a defense organization, has appointed

a Subcommittee on Industrial Health and Medicine, the duties of which are made to advise on the industrial health and medical aspects of national defense. This subcommittee also promulgates policies and suggests measures for coordinating all industrial hygiene activities for the national defense interpreted

Within the Federal Security Agency is the U S Public Health Service, containing the Division of Industrial Hygiene of the National Institute of Health. The Subcommittee on Industrial Health and Medicine has recommended that the Division of Industrial Hygiene of the National Institute of Health be given leadership in achieving the objectives previously cited. This is a very important consideration based on the fact that the Division of Industrial Hygiene has 26 years of experience in research and related problems, and a long discussion of the personnel, facilities, and relationships with national, state, and defense program agencies directly concerned with industrial hygiene problems and working conditions.

Realizing that the responsibility for the protection of the health of the many millions of workers lies finally with the states, the Division of Industrial Hygiene of the National Institute of Health, with the aid of the Federal Government under Title VI of the Social Security Act, has organized and is carrying out industrial hygiene services in more than 30 states. The work of these units is so integrated with that of the Division of Industrial Hygiene of the National Institute of Health that there now exists a nation-wide organization to serve effectively the national needs of workers in defense industries.

The Program On February 17 and 18 of this year, a conference was held for the purpose of developing a nation-wide program in industrial hygiene in defense industries. This conference, sponsored by the Division of Industrial Hygiene of the National Institute of Health, was attended by representatives from the various State industrial hygiene units, the Subcommittee on Industrial Health and Medicine of the Defense Committee, and prominent leaders in the field of industrial hygiene.

At this conference, the following pressing problems in industrial hygiene and its hazards were defined:

1 Further expansion in personnel, facilities, and funds of State industrial hygiene units and of the Division of Industrial Hygiene of the National Institute of Health.

2 Aid to military establishments, upon request of these establishments, in evaluating health hazards, and in the training of personnel.

3 Surveys of commercial shipyards, airplane plants, and establishments producing military vehicles and munitions, and the training of industrial hygiene personnel in these industries as needed.

4 Promotion of first-aid in the construction of industrial plants, especially those in isolated areas.

5 Toxicological investigations of materials vital to national defense, notable among which are toluol, trinitrotoluol, lead azide, and vinyl cyanide.

The conference recognized the importance of environmental sanitation surrounding isolated industrial areas, but was informed that this problem

dled by local health authorities with the aid of other divisions of
Public Health Service

Needle program finally adopted by the conference, and one now in effect,
augmented those working relationship between the Division of Industrial
into military, the Institute, the various state industrial hygiene units, and other
adults, and governmental and non-governmental, such as the U S De-
fit as the member, the Council on Industrial Health of the American Medi-
accustomed to industry, and labor The program being applied in each
safe for these health area has the following objectives

health and safe disease rates ation and control of the various health hazards resulting

The problem dusts, fumes, gases, vapors, and other materials
appear as a resion of advisory services to industry in connection with
chemicals will of new plants and the renovation of old plants, so that
toxic nature s for health and safety may be included in the plans
pressure of thotion of physical examinations and medical services for the
vigilance, so nr that the benefits of preventive and curative medicine may
workers Dr otly to their individual health problems
the most efficiol of communicable diseases among workers through a con-
women who oveloped in connection with the general public health services
so with a compy

These, in l
today Have l that the above program can best be fulfilled by supple-
problems? lities of state and local units through the expansion of the
vided by the Division of Industrial Hygiene of the National
alth Congress has made available recently additional funds

Fortiork and today there are several mobile units, each consisting of a
century, and an engineer, working in key defense industries, in cooperation
the applicate departments of health By July of this year it is planned to
preparedximately 20 such units in the field
industrial, work of these mobile units, the engineering personnel are con-
tions min, evaluating the working environment and recommending ways
to cor, for the control of any health hazards revealed by the investigation
he medical personnel, on the other hand, work very closely with local medi-
l organizations, such as the state committees on industrial health developed
by the Council on Industrial Health of the American Medical Association
These medical officers appraise present medical control services in industry
and recommend improvements in these services, where indicated The prob-
lem of personal relationships, or mental hygiene in industry, is emphasized
Plant management is informed, either directly or through the medical de-
partment, if one exists, of the importance of such provisions as periodic
inspection and appraisal of plant sanitation and occupational exposures, fol-
lowed by the adoption and maintenance of adequate control measures, the
provision of first-aid and emergency services, and the prompt and early treat-
ment for all illnesses resulting from occupational exposure are also recom-

mended Impartial health appraisals of all workers and the provision of rehabilitation services for the correction of defects are additional functions of a medical department which are advocated

The work of the Division of Industrial Hygiene has been aided in many of the defense industries by the splendid cooperation afforded it by the War Department The Secretary of War, in a circular memorandum dated March 18, 1941, has informed all the branches of the War Department employing civilians for industrial work and for those having direct jurisdiction over contract production, that the Division of Industrial Hygiene of the National Institute of Health has the necessary facilities for effectively rendering services for the protection of workers in these industries The Secretary of War recommended that full advantage be taken of the services available and has designated the Safety Officer, Office of the Chief of Engineers, to coordinate these activities As a result of this cooperative program, the Division of Industrial Hygiene of the National Institute of Health has already developed for the Section on Construction, Division of the Quartermaster General, minimum requirements for first-aid rooms and infirmaries in new construction projects

Time does not permit discussing the many other activities of the Division of Industrial Hygiene in the defense program Brief mention should be made of the Division's work in the training of personnel recruited for the mobile units functioning in the various states, the preparation and dissemination of both technical and non-technical information on the various phases of industrial hygiene, and the fundamental research work in progress at our laboratories on such substances as toluol, lead azide, and similar compounds vital to the defense program

RESPONSIBILITY OF THE MEDICAL PROFESSION IN THE PROGRAM

In the program for the protection of the health of workers in defense industries the medical profession bears certain responsibilities First, it is highly essential that physicians inform themselves further concerning occupational diseases, so that they will recognize such diseases more readily in the course of their practice It is very important that the private practitioner make this effort, in view of the fact that it is now well established that two-thirds of the workers in this country are not provided with either part-time or full-time services at the plant, but must seek such services from their private physicians The importance of obtaining an accurate and detailed occupational history from a patient cannot be overemphasized, in view of the fact that experience has shown that very often a man's occupation may have a real bearing on his health

It goes without saying, that the physician has a definite responsibility in reporting to the proper authorities the occurrence of occupational diseases among workers coming to his attention Physicians should adopt the same attitude toward the reporting of occupational diseases, which now exists with

regard to the reporting of communicable diseases. The medical profession can make still another important contribution in the field of industrial medicine, by stimulating the preemployment and periodic physical examination of workers in industry and by calling attention to the necessity of correcting those physical defects revealed by health examination. And, finally, the medical profession should strive to cooperate with *that* local health agency which is responsible for protecting the health of workers. The private practitioner, either as an individual or through his state and local medical organization, should utilize to the fullest extent the services which may be rendered by the official industrial hygiene division in his community.

In closing, it is desired to emphasize that the industrial hygiene program which has been briefly sketched has been created, not as an emergency improvisation, but as an integral part of our national life in the future. We must not forfeit the gains we have made for the sake of expediency. All of us, be we public health workers, private medical practitioners, engineers, chemists, industrial managers, or factory workers, must assume our share of the responsibility and coordinate all of our efforts, so that the men and women in our industries will attain a high level of efficiency and health.

THE CONTROL OF INFECTIOUS DISEASES IN RAPIDLY MOBILIZED TROOPS *

By A P HITCHENS, M C , U S A , F.A C P , *Philadelphia, Pennsylvania*

ASSEMBLING men from widely different environments, into the close contacts of military mobilizations favors the accelerated spread of infectious diseases and the development of explosive outbreaks. This means that carefully planned procedures for blocking their spread must be weighed against the exigencies of the military emergency. Whenever it is possible, and to the greatest extent possible, we want to counteract the passage of infection from the carrier to the susceptible recruit.

Zinsser¹ and others have suggested a scheme of "gradual mobilization" which would consist of regional aggregations of recruits in small groups of several hundred men in separate local camps for a few months before being concentrated in larger groups in distant areas for longer periods of intensive training. A discussion of the practicability of such an ideal plan would involve military administrative factors which might carry us beyond the scope of this paper. However, the obvious wisdom of this plan, from the medical point of view, requires that it have a prominent place in any consideration of military preventive medicine.

Whatever the method of mobilization, we have certain well tried procedures for use in combating infections. These are: strict examination of all men who are called up or volunteer, immunization, prompt recognition, isolation and treatment of contagious cases, immediate examination, continuous observation, and sometimes quarantine of contacts, rigid maintenance of a hygienic routine, adequate nutrition, and the sanitary control of the environment.

The men who are chosen in the present mobilization are being much more effectively examined than on any previous similar occasion. In addition to care in the detection of the acute contagious diseases serological and roentgen-ray examinations are eliminating many men who would be bad military risks.

The possibility of a rapidly changing and uncontrolled environment makes individual prophylaxis imperative to an Army. In certain directions our means for securing immunization have been refined and extended. In addition to the long established practice of vaccinating every man against typhoid fever and smallpox, many authorities are recommending the routine use of tetanus toxoid². Individual protection through artificially induced immunity will also be given in special cases where circumstances indicate it. Simmons³ has discussed this subject thoroughly in a recent paper on immunization in the Army. He has pointed out the value, in localized endemic

* Read at the Boston meeting of the American College of Physicians, April 24, 1941.

outbreaks, of the use of diphtheria toxoid and, in some instances, of scarlet fever toxin. For troops that may be sent to areas in the tropics, we have for consideration the possibility of vaccination against cholera, plague, and typhus fever. The War Department directed in February (1941) "that commanding officers take immediate action to vaccinate against yellow fever all military personnel now stationed in the tropical regions of the Western Hemisphere, including Panama and Puerto Rico" ⁴ The vaccine will also be given to all personnel ordered to those regions prior to their departure.

Although the long struggle to secure an effective vaccine against yellow fever has at last yielded excellent results, we still have the great challenge of the need for specific protection against a number of other serious infections, notably influenza. A board has recently been established by order of the Secretary of War for the investigation of influenza and other epidemic diseases in the Army. This board will "make immediate arrangements to utilize every scientific facility available in a concerted effort to control these diseases and to reduce their mortality to a minimum" ⁵ In my opinion the establishment of the various commissions, functioning under this board, is the most significant and important step ever taken by any Army to achieve the control of military disease hazards. We have apparently escaped a major epidemic of influenza this year, but this good fortune is only a reprieve. It seems highly probable that we shall be subjected to another pandemic in the not far distant future. The time available, before it comes, is being used to push vigorously the intensive research, already under way, on methods for improving our means of combating this disease whose devastating effects are aggravated by emergency mobilization.

Other illnesses, against which protection for men living under field conditions may be needed, are measles, mumps, meningitis, relapsing fever, malaria, gas gangrene, syphilis, and gonorrhea. The diseases which take epidemic form will receive special study by investigative teams which will be sent by the Surgeon General for temporary duty at military stations where and when there is a need. These teams are part of the organization referred to before in connection with the establishment of the board for the investigation of influenza and other epidemic diseases in the Army.

Syphilis and gonorrhea, which have always been responsible for serious loss of time and military effectiveness among troops are being better controlled than at any previous time. There are several reasons for this. One is an increase in the understanding of the diseases by the men themselves. Another is the changed attitude of higher authority and of medical and administrative officers generally in the matter of punishment. At present the infected soldier loses pay while he is away from duty because of his disease, but suffers court-martial only if he fails to report for treatment. Improvements in technic and drugs for therapy will lessen materially the loss of time and the sequelae of gonorrhea and syphilis during this mobilization.

Venereal disease is, of course, a civilian contribution to our armed forces. Therefore the organization of the home front defense against these major

causes of disability by Surgeon General Thomas Parran is a source of profound optimism. Working in close cooperation with the Army commanders, with the American Social Hygiene Association, local health, welfare and public safety officials and all other interested groups and individuals, a coordinated plan is already functioning which will reduce the sources of syphilitic and gonorrheal infection among our troops. Moreover the work initiated during this mobilization will have a lasting effect. The administrative innovations and the scientific research made possible by the concentrations of men in camps are merely the result of an acceleration of the country wide campaign initiated some years ago by the Surgeon General of the Public Health Service to rid our land of one of its most depressing shadows. The Army will take full advantage of this opportunity to aid in speeding up this great work.

The more highly efficient methods for immediate diagnosis and especially for treatment will result not only in lowered mortality from the acute infectious diseases, but will also serve, it is believed, to reduce the incidence of infections. The latter may be accomplished through shortening the duration of exposure to the sick and through a curtailment of the infectiveness of carriers. Everyone knows how completely the sulfa-group of drugs is changing the attitude of our internists toward severe infections due, notably, to virulent streptococci, pneumococci and meningococci. Physicians are confident now that a high death rate will result only from some interference with early treatment.

Other factors which will help in improving resistance to infections are the greatly enlarged knowledge we now have of nutrition and the channels provided for the application of that knowledge. A sub-committee of the National Research Council has been dealing since early in July 1940 with the nutrition problems of the Army and Navy.⁶ Our Army is already the most abundantly fed in the world, but it is believed that centrally regulated menus to assure a balanced ration, the more precise specifications for vitamin requirements, and improved forms of concentrates now available, will result in higher resistance to disease and greater physical endurance. Vitamin B fortified flour and bread, and vitamin D enriched pasteurized milk are examples of the products already in use.

Although we derive so much assistance from these measures which help in producing and increasing both specific and general resistance to infections, we still have to rely on rigidly controlled environmental sanitation in attempts to avoid the most serious of the health hazards which arise during the training period. The group of diseases which take heaviest toll among those for which we have no specific immunizing agents are the upper respiratory infections—bronchitis and pneumonia, both primary and secondary to influenza, measles and other diseases. Of the grand total of admissions for disease in the Army during 1918, and 1919, bronchitis, pneumonia and influenza represented one-third, and were the cause of 80 per cent of all deaths due to

disease In addition to these three, every medical officer knows of the tremendous loss of time and the expense and suffering resulting from outbreaks of common cold, tracheobronchitis, measles, mumps, and meningitis It will be noted that every one of these diseases may be spread through the air Our ideas concerning the spread of infection by droplets containing infectious material from the nose and throat have undergone marked changes as a result of the researches of William Firth Wells in regard to air-borne infections Although no doubt respiratory infections are spread by the large droplets examined by Flugge⁷ in 1898, the range of transmission of these larger droplets is limited strictly by the force of gravity That type of spread is not essentially different from direct contact Wells has demonstrated clearly that the residues of smaller droplets may float in the air for long periods over distances far in excess of those once believed to be possible⁸ These droplet nuclei which form from expelled droplets of 0.1 mm and less in size may carry infectious material which remains viable for periods long enough to infect other individuals within the enclosure

Wells has shown that ultra-violet irradiation is lethal to organisms of the droplet nuclei which are in the atmosphere His well controlled experiments show clearly two things which may hold the key for checking the spread of air-borne infections, namely (1) infectious agents (for example, influenza virus, streptococci, and other pathogens of the naso-pharynx) do survive in the droplet nuclei which are transported by air currents through enclosed spaces and (2) the air can be disinfected by ultra-violet radiation

Both of these essential factors—that is, that infection is transmitted through the atmosphere and that the disinfection of the air can be accomplished by ultra-violet radiation—have been demonstrated repeatedly under controlled experimental conditions Our knowledge of specific requirements for large scale application of this knowledge is being rapidly developed However, there is enough evidence now at hand to indicate prompt and extensive use of ultra-violet radiation for the disinfection of air where there are concentrations of people as in auditoriums, barracks, and mess halls

Nobody thinks that radiant disinfection of air is the one and only answer to the control of respiratory infections It cannot be expected to affect materially those organisms in the large droplets expelled by coughing, sneezing, and talking which can and do infect persons in close contact with the origin of infection However, ultraviolet radiation, if applied for the proper length of time and in the necessary amounts, is lethal to the infectious material in the droplet nuclei which float about in the air and which can be rapidly dispersed by air currents

Wells is making a careful study (which is now in its fourth year) of the possibility of reducing the seasonal incidence of measles, mumps, chickenpox, and the other childhood diseases, by sterilization of the air under practical conditions This work is being done in some of the public schools of Swarthmore, Pennsylvania, and in the Germantown Friends School of Phila-

delphia His early findings, as yet unpublished, are strongly indicative of the usefulness of ultra-violet radiation in reducing the incidence of air-borne infections in classrooms That disinfection of the air in army barracks, air-raid shelters, and such places where war and other circumstances force extraordinary crowding of susceptibles in semi-confined atmospheres would be equally or even more effective is a logical inference In my opinion, there is sufficient evidence already available to warrant the practical installation immediately of ultra-violet lights in structures where mobilized men are quartered, and where they are accustomed to congregate, in order that observations under military conditions may be made

In conclusion, in so far as the military emergency will permit their application, the following procedures are available to us for the control of infectious diseases in rapidly mobilized troops

- 1 Careful examination of every registrant for evidence of such conditions as incipient or latent tuberculosis, syphilis, and other diseases which men may have when selected or enlisted

- 2 Immunization against smallpox, the typhoid fevers, tetanus and yellow fever, with extension of individual prophylaxis under specific circumstances against diphtheria, scarlet fever, measles and possibly against influenza

- 3 Avoidance when feasible of sudden geographic shifts during seasons in which the incidence of certain diseases such as pneumonia is known to be high

- 4 Maintenance of a high quality of hygienic regimen with special emphasis on fortification with vitamins

- 5 Avoidance of excessive fatigue and exposure during the hardening period

- 6 Continuation of the well-tested methods for the control of the water supply, use of pasteurized milk exclusively, and exacting inspection of meats and other foods

- 7 Careful attention to spacing of beds in squad rooms and hospitals and to ventilation with a thorough and open-minded trial of radiant disinfection of the air under controlled military conditions

At no previous period in the history of our Army has there been available to us so great a variety of effective methods for controlling the morbidity and mortality resulting from infections Certainly, at no previous period has there been a more efficiently organized plan for the utilization of current knowledge and for the expansion of such knowledge This is clearly revealed in the following statement made by Surgeon General James C Magee when he recommended the establishment of the board for the investigation of influenza and other epidemic diseases in the Army "The establishment of this board will make available to the Army the scientific resources of the country to assist in the program for the control of influenza and other epidemic diseases which will undoubtedly arise in our expanding Army" "

BIBLIOGRAPHY

- 1 ZINSSER, HANS. On the medical control of mobilization, *Mil Surgeon*, 1940, lxxxvii, 214-221
- 2 JORDAN, E P, and HALPERIN, GEORGE Tetanus toxoid for prophylaxis, *War Medicine*, 1941, 1, 227-246
- 3 SIMMONS, JAMES Immunization against infectious diseases in the United States Army, *South Med Jr*, 1941, xxxiv, 62-67
- 4 Circular Letter No 9, Office of the Surgeon General, War Department, February 12, 1941
- 5 Circular Letter No 3347-1, Office of the Surgeon General, War Department, January 27, 1941
- 6 WILDER, RUSSELL M Nutrition planning for the national defense, *War Medicine*, 1941, 1, 143-157
- 7 FLUGGE, C Ueber Luft Infektion, *Ztschr f Hyg u Infektionskr*, 1897, xxv, 179
- 8 WELLS, W F, and WELLS, M W Air-borne infections, *Jr Am Med Assoc*, 1936, cvii, 1698-1703, 1805-1809
- 9 Circular Letter, No 3347-1, Office of the Surgeon General, War Department, December 27 1940

THE MECHANISMS OF PERIPHERAL CIRCULATORY FAILURE*

By CARL J WIGGERS, M D , D Sc , F A C P , *Cleveland, Ohio*

ORIENTATION

THE capillaries constitute the keystone of the circulation, in the sense that maintenance of an adequate capillary flow is essential for the proper exchange of respiratory gases, electrolytes and water, foodstuffs and waste products. The rate of capillary blood flow is regulated (figure 1) by the pressure in the small supplying artery (*A*), by the size of muscular arterioles (*B*), possibly by active changes in size of capillaries (*C*), by pressure of surrounding tissues (*D*), by the pressure in the small venules (*E*), and by the viscosity of the blood itself.

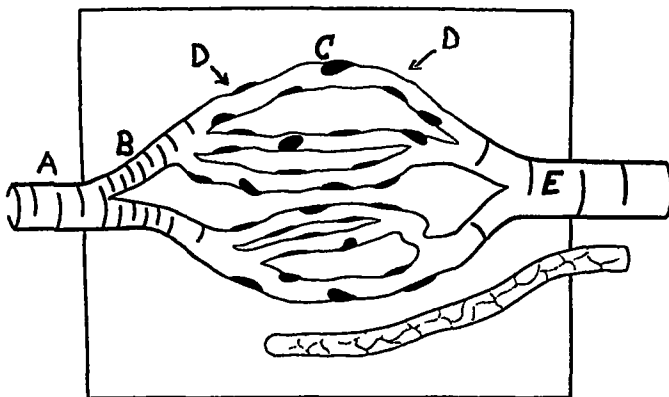


FIG 1

Circulatory failure, in its broadest sense, develops whenever the driving pressure in small arteries (*A*) is not adequate to overcome the composite resistance (*B*, *C*, *D*, *E*) offered in capillary districts, and the blood flow therefore decreases. Circulatory failure may exist with normal, low or high arterial pressures. For example, it occurs in chronic congestive heart disease, even while arterial pressures still remain within normal ranges, owing to the high resistance offered by venous pressure at *E*. It develops in conjunction with chronic myocardial depression and follows coronary occlusion, pericardial effusions and Pick's disease, even when arterial pressure is maintained by compensatory constriction. Two peripheral factors operate: the higher venous pressure at *E* and the reduced caliber of vessels at *B*. Circulatory failure occurs during hypertension when the pressure in

* Morning lecture presented before the American College of Physicians, Boston, April 22, 1941

From the Department of Physiology, School of Medicine, Western Reserve University, Cleveland, Ohio

TABLE I
Symptom Complex of Acute Circulatory Failure (Shock)

General Appearance and Reactions	Skin—Mucous Membranes	Circulation	Miscellaneous
Countenance drawn—anxious lusterless eyes sunken eyeballs ptosis of upper lid (slight) upward rotation of eyeball (slight)	Skin pale, livid, ashen gray slightly cyanotic moist, clammy mottling of dependent parts loose, dry, inelastic, cold	Superficial Veins small, invisible Failure to fill on compression or massage Inconspicuous jugular pulsations	Respiration Variable but not dyspneic Usually increased rate, decreased depth Occasional deep sighs
Neuromuscular Tremors, twitchings Restlessness or listlessness Muscular weakness Weak voice Apathy Delayed cerebration Depressed sensibilities Depressed visual and auditory reflexes Depressed tendon reflexes Swallowing difficulty	Mucous Membranes pale, livid, slightly cyanotic	Heart Impulse and sounds, feeble Rate, usually rapid	Temperature Apt to be sub-normal
	Conjunctiva glazed, lusterless	Radial Pulse Rapid Small volume "Feeble," "thready"	Basal Metabolic Rate Reduced
	Tongue dry, pale, shrivelled, parched	Brachial Blood Pressures Lowered Pulse pressure small	General but Variable Symptoms Thirst Vomiting Diarrhea Oliguria
		Retinal Vessels Narrowed	
		Venous Blood Reduced O ₂ content Hemoconcentration frequent (?) usual (?) Coagulation time reduced	

supplying arteries (*A*) is not high enough to overcome the reduction in size of arterioles (*B*). It occurs in various forms of hypotension because the pressure head in *A* is unable to maintain a normal rate of flow through the capillaries. The causes of such hypotension may be (1) Primary cardiac failure (e.g., sudden profound slowing or acceleration of the heart beat, abrupt development of conduction disturbances, myocardial depression through toxins, anoxia, anesthetics, etc., deletion of contacting fibers as during coronary occlusion and alternans) (2) Secondary cardiac failure due to impairment of ventricular filling as happens in pulmonary embolism, large pericardial effusions, sudden assumption of the erect position, prolonged standing, etc. (3) Generalized arteriolar dilation of central origin (emotional syncope), of reflex origin (epigastric or jaw blows in pugilism) and from interruption of normal sympathetic pathways (splanchnic nerve section, spinal anesthesia)

All of these types are advisedly differentiated from a rapidly progressive form of peripheral circulatory failure, characterized by progressive decline of arterial as well as central venous pressure which is designated surgical, traumatic, or toxemic shock

SYMPTOMATOLOGY AND CLASSIFICATION

The clinical signs and symptoms of this type of peripheral circulatory failure vary somewhat under different circumstances. They can include any or all of the features gathered from various clinical reports and conveniently summarized in table 1.

Concurrent with development of the views (1899) that traumatic and surgical shock are fundamentally of peripheral origin, internists began to postulate a similar etiological basis for types of circulatory failure that belong more strictly within the province of medicine. The more important associations with various diseases are shown in the following table.

TABLE II
Causes of Peripheral Circulatory Failure (Shock)

Group I	Group II	Group III
<i>Surgical</i>	<i>Borderland</i>	<i>Medical</i>
Anesthesia	*Hemorrhage	Infections and intoxications
*Operations	*Gastrointestinal perforations	Diphtheria
*Trauma	Peritonitis	Influenza
*Burns	Pancreatitis	Pneumonia
Exposure	Severe dehydrations	Scarlet fever
Freezing	*persistent vomiting	Meat poisoning
*Strangulated hernia	*diarrhea	*Cholera
*High intestinal obstruction	Gas bacillus infections	*Diabetes
		Adrenal cortical deficiency
		Anaphylaxia (?)
		Thymic death (?)
		Status lymphaticus (?)

* Cases in which loss of blood or plasma plays important, dominant and perhaps sole rôles

In setting up such a concept of peripheral circulatory failure in medical practice, internists were aware, of course, that acute cardiac disturbances may develop concurrently and that death may be due to primary cardiac or respiratory failure.

THE KEYSTONE OF PERIPHERAL CIRCULATORY FAILURE

In reviewing the mechanisms by which such circulatory failure is started and those by which it progresses, it is advisable to begin with facts upon which all seem to agree. Reduced venous return to the heart (decreased effective venous pressure) and capillary stagnation are the *sine qua non* of toxic and other forms of shock.

It seems paradoxical—but it is true—that the proximate cause of the hypotension which develops progressively is due to diminished cardiac output. This occurs, not because the myocardium is depressed, but because an insufficient volume of blood returns to the heart. Decreased systolic discharge accounts for the feeble heart sounds and apex beat, the decline in blood pressure, the small pulse pressure and the feeble, thready pulse. The empty

peripheral veins are visible evidences of reduced venous return from the limbs

POSSIBLE CAUSES OF THE REDUCED VENOUS RETURN

Obviously, a satisfactory explanation of the reduced venous return would go a long way in explaining the cause of peripheral circulatory failure. Fundamentally, it can only be attributed to two causes (1) reduction in the circulating blood volume or (2) sequestration of blood in capillaries or sinusoids so that it is virtually removed from effective circulation. Stated in another way, there may be too little blood to fill the vascular system, or the vascular system may be too large for a normal volume of blood.

An actual reduction of blood volume occurs after external or internal hemorrhages, also in conditions in which dehydration, protracted vomiting, prolonged diarrhea, drainage of secretions or of serum from wounds and burns, traumatic damage to capillaries, etc. are a prominent feature. These are demarcated by an asterisk in table 2. However, such loss of fluid is not always obvious in toxic or infectious types of circulatory failure, with which the internist frequently has to deal. Nevertheless, on the basis of studies on blood volume in animals and man and examination of organs post mortem, many believe that considerable quantities of plasma are abstracted from the blood stream in these conditions, as well. We may accept this provisionally, but reserve the privilege of returning to this phase of the problem at a later time.

The bulk of experimental evidence indicates that when and if such transudation of plasma occurs it is necessarily preceded by capillary stasis and perhaps by intrinsic changes in capillary permeability. Inasmuch as the capacity of the capillary beds is increased, it also acts to withdraw blood from active circulation, thus creating a second way for reducing venous return. We shall, therefore, advance our analysis of the peripheral mechanisms by which circulatory failure occurs if we examine systematically the ways in which such capillary stasis may occur and, if possible, indicate which of these appears the most probable.

Four initiatory mechanisms have been suggested and each can be supported by experimental evidence. They are (1) primary arteriolar dilatation, (2) primary arteriolar constriction, (3) primary atony and dilatation of capillaries and (4) primary failure of some veno-pressor mechanism.

PRIMARY ARTERIOLAR DILATATION

The arterioles are the terminal stopcocks of the arterial tree which regulate the volume flow of blood from arteries into capillaries. Ever since the pioneer experiments of Claude Bernard on the salivary glands, physiological evidence has supported the thesis that arteriolar dilatation increases capillary pressure and volume. Unused capillaries become patent, the filtration and flow of lymph are augmented and the organ or district affected increases in

volume This is also the fundamental reaction in inflammatory hyperemia As a result of such arteriolar dilatation, the venous flow from an organ at first increases, but if widespread territories are involved, the arterial pressure declines and venous flow is reduced Meanwhile a volume of blood equal to that which "bleeds into capillaries" is prevented from returning to the heart It is not difficult to calculate that such an abstracted volume may be quite sizeable It can be argued that such withdrawal occurs essentially from the arterial rather than the venous side However, the question cannot be settled by such theorizing because circulatory conditions are highly complicated In brief, we may state that the effect of such primary arteriolar dilatation on total venous return depends upon the extent to which compensatory translocation of fluid from various blood reservoirs, such as the spleen, liver, skin, and perhaps the lungs, takes place Thus, maximal dilatation of arterioles by nitrites leaves the total return flow of venous blood unaltered or may even increase it, whereas, similar dilatation by histamine is said to reduce it

PRIMARY ARTERIOLAR CONSTRICTION

Many, but by no means all, available experimental results suggest that the arterioles are constricted in various shock-like states Hence, the conclusion that arteriolar constriction is primarily responsible for capillary stasis and reduced venous return

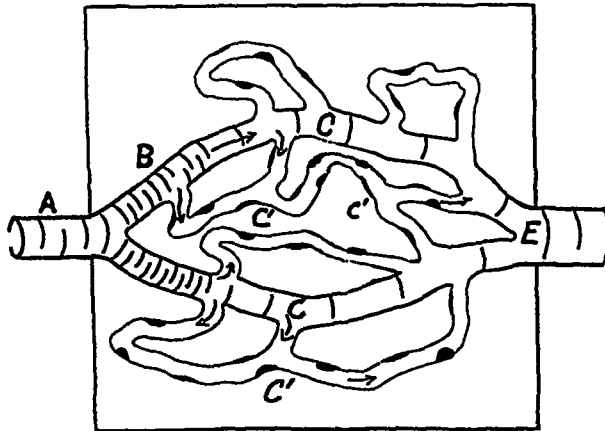


FIG 2

Since arteriolar contraction (figure 1, B) primarily reduces capillary pressure and capacity in any territory and shrinks the organ or tissue affected, some mechanism must exist which produces the capillary dilatation Secondly, two possibilities exist (1) The decreased capillary flow following initial arteriolar constriction may cause anoxia or asphyxia in capillaries, which relaxes and increases the permeability of their walls The concept assumes with Krogh and his school that capillaries have the power of independent contractility, it ignores the evidence of Clark and Clark and of

Chambers and Zweifach that they do not possess such a physiological property

2 If, as Zweifach¹ has recently claimed, the main nutritional capillaries are not directly interposed between the arteries and veins, as shown in figure 1, but represent a series of shunts, as is schematized in figure 2, an extension of arteriolar constriction to the main A-V capillary (C) would shunt blood into the real capillaries (C), causing the expansion of those in use and the opening of others not previously in action. It is thus possible, from a dynamic viewpoint, to postulate capillary stagnation after arteriolar constriction either as a passive process or as an active relaxation of capillaries themselves

PRIMARY CAPILLARY DILATATION

Many chemical substances and tissue extracts, upon intravenous injection, cause circulatory changes which resemble shock. They include certain lymphagogues studied by Heidenhain (extracts of muscles, and crayfish, peptones, etc.), decomposition products or extracts of the intestinal mucosa, liver, muscle, etc., bacterial toxins, snake venoms, histamine, adenylic acid, etc. Most of these are unquestionably capillary poisons which alter the turgor and permeability of capillary walls, thus causing stasis and transudation of fluid. Moreover, various substances such as liver, minced muscle, etc., upon introduction into the peritoneal cavity lead to hemoconcentration, decline in blood pressure, and reveal obvious congestion of capillaries and edema of organs on postmortem examination (Moon). These and other experimental evidences suggest that as yet unidentified chemical substances formed during high intestinal obstruction, rupture or perforation of the gastrointestinal tract, toxins, infections, etc., may act on capillaries in a similar manner and produce capillary congestion, edema, and hence a reduced venous return.

Time is lacking to consider the evidences of guilt or innocence of the various agents suggested. It may be emphasized, however, that failure to identify the substance is not proof of its nonexistence. Indeed, a variety of agents, rather than a common one, may be concerned in various toxic states. It may not necessarily be a single identifiable agent but, as is apparently the case of iennin, may require an activating agent or involve participation of endocrine glands like the adrenal cortex. This would explain the development of similar states of shock during cortico-adrenal insufficiency.

FAILURE OF A VENOPRESSOR MECHANISM

The ultimate force which returns blood to the heart is, of course, the pressure component still available after blood has been driven through the capillaries. The magnitude of this force is not large, indeed, were it not for a negative pressure within thoracic veins it would not suffice to raise blood to the abdomen in a standing position. The mechanisms by which sub-

subsidiary forces and return is not too clear, but it is commonly believed that they include (a) extravascular support offered by elasticity of tissues, contraction and tonus of muscles, etc., (b) pumping action of respiration, and, (c) active venomotor changes in venules and small veins

The suggestion that peripheral circulatory failure begins on the venous side of capillary beds presupposes one of two opposite actions

1 The small venules rather than the capillaries may dilate primarily. This may be due either to a relaxation of their muscular elements and/or to a reduction of pressure in surrounding tissues. Starling² and Y. Henderson³ have both suggested that the decrease in tonus of skeletal muscles during shocklike states may remove such a supporting force. However, most of the evidence suggests that reduction in skeletal muscle tonus could be only of subsidiary importance. Shock does not develop during paresis or myotonia gravis, furthermore stagnation does not appear to occur in limb vessels during toxic shock. However, cessation of intestinal movements, loss of tonus in viscera, etc. may conceivably be more potent. Granting the operation of such a mechanism, the capillaries would fill as a result of the dissipation of pressure transmitted from arterioles to the tissues.

2 The small venules may on the contrary constrict. This would trap blood in capillaries, increase resistance to pressure transmission and thus diminish the force which returns blood to the heart.

DISCUSSION

The foregoing brief summary indicates the ease with which plausible explanations can be set up to account for the capillary stasis and reduced venous return. It is also possible to prove the correctness of each of these concepts by a judicious selection of experimental evidence. The real difficulty consists in deciding which of the postulated views, if any, is correct. This cannot be done by stating one's own impressions (or prejudices) or by balancing opinions of authoritative investigators. Unfortunately the question can also not be decided by a critical reconsideration of experimental results instead of conclusions based on them. There are enough of these, if accepted at par, to make all of these views untenable. This dilemma may be illustrated by applying experimental facts to the two favored theories regarding the initiating factors in shock.

In order to implicate arteriolar constriction as an initiating factor it is necessary to demonstrate (1) that such constriction exists early in shock and involves widespread areas and (2) that it is of sufficient intensity and duration to cause the sequestration of blood in capillaries. In my judgment, neither has been proved. The experimental evidence that vessels are initially constricted is frequently quoted, that which indicates that they are dilated is conveniently ignored (cf. Bartlett,⁴ Morrison and Hooker,⁵ Penfield,⁶ Forward and Perme⁷). Of the experimental results indicating that constriction

occurs (Erlanger, Gasser et al,⁸ Sollmann and Pilcher,⁹ Gesell,¹⁰ Cattell, Jr¹¹), none proves that it is of sufficient intensity to increase the total resistance to the runoff from the aorta. The only evidence we have indicates that peripheral resistance decreases (Dingle, Kent, Williams, Wiggers¹²). Furthermore, experimental and clinical hypertension in which the peripheral resistance is greatly increased, does not eventuate in shock, and no one has succeeded in producing shock by prolonged vasoconstriction following stimulation of afferent nerves. Large unnatural doses of adrenalin, if long continued, lead to shock, but only after withdrawal of the agent. In our experience, the abrupt decrease in coronary flow which occurs when adrenalin injections are stopped often causes death from cardiac, not peripheral, failure. This is also the case when the aorta is compressed for a long time and suddenly released. Freeman¹³ reports reduction in blood volume following more reasonable doses of adrenalin, but this could not be confirmed by Hamlin and Gregersen¹⁴. However, granting such decrease, it remains an inference that vasoconstriction was the cause. Prolonged use of adrenalin has a deteriorating effect on the heart and perhaps on capillaries as well.

To summarize, a critical consideration of existing experimental results does not convince me that primary arteriolar constriction, induced by nervous or humoral mechanisms can be an important initiating factor in peripheral circulatory failure.

It remains to square this conclusion with the obvious constriction of surface vessels which gave rise to the vasoconstrictor concept of shock among clinicians. We may accept such constriction as demonstrated beyond question. However, attention may be directed to the fact that a similar constriction accompanies many forms of visceral pain which do not ordinarily eventuate in shock, among them, gastric, biliary and ureteral colic. Furthermore, admitting a degree of constriction in skin and muscles to the point of tissue asphyxiation, it is curious that the pathological changes in capillaries described as characteristic of shock are not found in somatic structures. Obviously, the scientific evidence does not fit together in implicating vasoconstriction as a cause of capillary stasis.

Dilatation of capillaries through humoral agents, followed by transudation of plasma must certainly be considered a probable mechanism in forms of shock in which obvious loss of blood or fluid cannot be held accountable. It is necessary, however, to make certain reservations with regard to the probable agent. The unknown agent (or agents) must be potent and exert a sustained action, it must affect rather extensive capillary territories and must also have a certain selectivity, for the somatic capillaries are apparently unaffected.

Personally, I challenge a common view that anoxia or asphyxia of a degree which is probable, could produce the severe reactions. Prolonged anoxia, e g, at high mountain tops, produces very serious symptoms in animals and man, but not those of shock. The extreme passive congestion of viscera attending chronic heart disease is attended by a marked anoxia for

many years without evidence of shock. Recent observations of Maurer¹¹ have proved that general anoxia increases lymph flow, but inasmuch as, in the body, this is returned by lymphatic ducts to the venous stream, such increased transudation cannot contribute to the reduced venous return.

It is profitable to reconsider whether the circulatory volume is as significantly reduced in toxemic shock as is commonly believed. The idea—a very old one—was suggested by the apparent thickness of the blood after death from certain forms of shock, e.g., after cholera. It was supported by data that the specific gravity, plasma protein, red cell counts and hemoglobin increase in various forms of shock. It is supposed to have been demonstrated beyond question by use of dyes and other substances, suitable for determining blood volume. Results so obtained must be relative rather than absolute, since dyes and other colloidal substances would pass through leaking capillaries and involve an error unless they were returned by lymphatic channels to the circulation. Furthermore, the translocation of blood from various depots has not been adequately considered. Gregersen informs me that, in his experience, blood volume determinations are treacherous unless animals have been previously splenectomized. How much of the hemoconcentration now regarded as an index of depleted plasma volume is due to addition of red corpuscles from the spleen and surface capillaries rather than abstraction of plasma through capillary walls?

The evidences of edema and serous effusions on autopsy would seem to constitute the most conclusive evidence that circulatory fluid is lost. But such studies are qualitative only, they cannot tell how much plasma is lost. It is impossible to measure or calculate the volume of edema fluid in tissues and compare it with the compensatory volume placed in circulation by contraction of the spleen, skin vessels, etc., not to mention fluid reabsorbed in other regions. The suggestion that some of the edema seen in tissues, post mortem, may have developed during the process of death or even after death, will perhaps sound fantastic to pathologists. However, it ought to be made and investigated, particularly since pulmonary edema and large serous effusions are seen so commonly on autopsy, while signs of their occurrence are strikingly absent during the course of experimental or clinical shock. Have clinicians missed important signs of shock or do the autopsy findings show conditions which did not exist during life?

A few words may be added in regard to the concept that arteriolar dilatation represents an initiating event. The concept has been generally abandoned, largely because it had become so definitely linked with the theory of failure or exhaustion of the vasomotor center. The latter appears to have been definitely disproved. However, it is not necessary to assume, particularly in toxemic forms of shock, that arteriolar dilatation is necessarily dependent on failure of a central or peripheral nervous mechanism, it could be caused by action of the same humoral agents which are generally believed to act on capillaries. Indeed, it is not improbable that, if any such agent exists, it would affect arterioles, capillaries and venules alike. Sir Thomas

Lewis, with greater wisdom than shown by others, refers toxic actions to the "minute vessels," which presumably include arterioles

The argument that primary arteriolar dilatation is excluded by the fact that decrease in cardiac output precedes the fall in blood pressure is not a valid one. It is conceivable, and indeed probable, that primary dilatation in fairly extensive regions would be compensated, *pari passu*, by cardiac acceleration and arteriolar constriction in other regions through sinus caroticus and aortic reflexes. This happens very quickly in normal subjects after inhalation of amyl nitrite, pressures are restored in 1 to 2 minutes, while vessels remain dilated in certain regions. Compensatory constriction might operate to do more than restore a normal total aortic resistance. Enough blood may be mobilized from the spleen, liver and skin so that it not merely compensates for any local reduction in venous flow from organs involved, but it may even supply a larger return volume for the accelerated heart to pump. Failure to grasp the many-sided factors involved in dynamic adjustment of the circulation has been responsible for much illogical discussion on the part of investigators not sufficiently familiar with elementary aspects of hemodynamics. According to this conception, a different rôle would be assigned to the generalized constriction of skin vessels during peripheral circulatory failure. They probably constitute a compensatory mechanism by which blood from the skin plexuses is placed in circulation in the viscera rather than being a provocative cause of shock itself.

A few in my audience may recall that similar conclusions were reached as a result of personal investigation¹⁰ of traumatic shock in 1918. With broader experience, I am ready to grant that the thesis that shock is initiated by a primary vasodilatation was not as crucially demonstrated as I then believed. However, the changes in the form of aortic pressure pulses then presented have never been controverted, or explained more satisfactorily. I hold no brief for this or any other conception as to the factor which initiates peripheral circulatory failure, but insist that it is scientifically inadvisable to cast the hypothesis aside too hastily.

INITIATING, SUSTAINING AND PRECIPITATING FACTORS

Following a suggestion of Gesell,¹⁰ it has become customary to differentiate between initiating and sustaining factors in shock. In addition, we must consider the probability that there may be a precipitating factor which determines whether the changes inaugurated and sustained lead to recovery or death. All experimenters who have investigated the shock problem in animals can attest to two impressions. (1) After application of a procedure designed to produce shock, animals may display a moderate imbalance of the circulation for hours. From this they either recover completely or quite suddenly go into a state of irreversible circulatory failure. (2) A standard laboratory procedure which produces shock in the majority of animals, fails to do so in a considerable number. The question, therefore, logically arises

whether in our zeal to implicate capillary stasis, reduced venous return, decreased circulation volume, etc., we may not have overlooked precipitating factors which may not involve the peripheral circulation at all, or only indirectly

Recent advances in our understanding of circulatory regulation have shown the existence of many mechanisms by which the circulation adjusts itself in health and disease so that arterial pressure is maintained at reasonably standard levels and blood flow is adjusted to the needs of various tissues in different states of activity. These comprise both direct and reflex actions. Additional and hitherto unsuspected mechanisms operating toward these ends are still in the process of discovery. Without prejudice to the view that capillary stagnation, transudation and decrease in circulating volume initiate the changes responsible for peripheral circulatory failure, the possibility ought to be investigated whether a failure or incoordination of the numerous stabilizing mechanisms may not constitute a vital precipitating factor. I understand that this project is under investigation in other laboratories by workers trained in the technic of such studies. These are among the encouraging signs that a shift in emphasis has begun in the experimental study of the problem of peripheral circulatory failure.

Aided by a grant from the Commonwealth Fund, our laboratory has likewise initiated investigations in these directions. It would be premature and wearisome to enlarge upon all the trends of approach that have suggested themselves. However, we may briefly indicate one trial approach which intrigues us at the present time. Preliminary experiments recently reported by Werle and Cosby¹⁷ showed that when the blood pressure of a dog is kept at a level of about 65 mm for 2 hours or more by bleeding or plasmapheresis, reinjection of all the fluid abstracted may either eventuate in complete recovery or, after very temporary benefit, may result in complete circulatory collapse. A study of the forms of the aortic pressure pulses in dogs that fail to recover suggests that either the natural myocardial or aortic reactions to a restored circulatory volume may have defaulted. Consequently, we are reinvestigating the possibilities that the mechanisms which adapt aortic size and elasticity to varying volumes and pressures of blood, or aberrant responses of the myocardium following prolonged diminution of coronary flow, may be at fault.

REFERENCES

- 1 ZWEIFACH, B. W. Structures and reactions of small blood vessels in Amphibia, *Am Jr Anat*, 1937, **lx**, 473
ZWEIFACH, B. W. Character and distribution of blood capillaries, *Anat Rec*, 1939, **lxviii**, 475
- 2 STARLING, E. H. Surgical shock, *Arch méd belges*, 1918, **lxvii**, 369
- 3 HENDERSON, Y. Volume of circulation and its regulation by venopressor mechanism, *Jr Am Med Assoc*, 1931, **xcvii**, 1265
HENDERSON, Y. Muscle tonus, intramuscular pressure and venopressor mechanism, *Am Jr Physiol*, 1936, **cxiv**, 261

- 4 BARTLETT, W An experimental study of the arteries in shock, *Jl Exper Med*, 1912, *xx*, 415
- 5 MORRISON, R A, and HOOKER, D R Vascular tone and the distribution of the blood in surgical shock, *Am Jr Physiol*, 1915, *xxvii*, 86
- 6 PENFIELD, W G Treatment of severe and progressive hemorrhage by intravenous injection, *Am Jr Physiol*, 1919, *xlvi*, 121
- 7 FORWARD, D D, and PERVE, L J Changes in total peripheral resistance during experimental shock, *Proc. Soc Exper Biol and Med*, 1922, *xx*, 190
- 8 ERLANGER, J, GSELL, R, and GASSER, H S Studies in secondary traumatic shock I Circulation in shock after abdominal injuries, *Am Jl Physiol*, 1919, *xlix*, 90
- 9 PILCHER, J D, and SOILMANN, T Studies on the vasomotor center. The effects of hemorrhage and reinjection of blood and saline solution, *Am Jr Physiol*, 1914, *xxxv*, 59
- 10 GSELL, R Studies on the submaxillary gland IV Comparison of the effects of hemorrhage and of tissue-abuse in relation to secondary shock, *Am Jr Physiol*, 1918, *xlvi*, 468
- 11 CATTELL, McK., JR., quoted by CANNON, W B Traumatic shock, 1923, Appleton Co, New York, p 20
- 12 DINGLE, J T, KENT, G T, WILLIAMS, L L, and WIGGERS, C J Study of alleged quantitative criteria of vasomotor action, *Am Jr Physiol*, 1940, *cxxx*, 63
- 13 FREEMAN, N E Decrease in blood volume after prolonged hyperactivity of the sympathetic nervous system and sympathectomy on the plasma volume of the cat, *Am Jr Physiol*, 1933, *ciii*, 185
- 14 HAMLIN, E, and GREGERSEN, M I The effect of adrenaline, nembutal and sympathectomy on the plasma volume of the cat, *Am Jr Physiol*, 1939, *cxxv*, 713
- 15 MAURER, F W Effects of decreased blood oxygen and increased blood carbon dioxide on the flow and composition of cervical and cardiac lymph, *Am Jr Physiol*, 1940, *cxxxi*, 331
- 16 WIGGERS, C J Shock and circulatory failure following trauma, *Am Jr Physiol*, 1918, *xlvi*, 314
- 17 WERLE, J M, and COSBY, R S Initiation of shock through loss of blood or plasma, *Am Jr Physiol*, 1941, *cxxxiii*, 299

THE PNEUMONIA OF FRIEDLÄNDER'S BACILLUS *

By L A JULIANELLE, *St Louis, Missouri*

THAT Friedlander's bacillus may be the cause of massive infections of the lung was first pointed out in 1882 when its discoverer assigned to it the chief etiological rôle¹ in the pathogenesis of lobar pneumonia. The expansiveness of this conclusion immediately precipitated a controversy² which at the present time seems unnecessarily acrimonious since the statement erred not so much in principle as in accuracy, requiring, therefore, merely modification, and not rejection as recommended on the ground that the organism is involved in pneumonia only in the capacity of a secondary invader. It was Weichselbaum³ who subsequently clarified the dispute when confirming the concept of earlier workers that pneumococcus is indeed the most frequent agent in primary pneumonia, he nevertheless demonstrated that Friedlander's bacillus may also induce a similar pulmonary condition, but in considerably reduced ratio. This constitutes today the universally accepted concept, although occasional investigators⁴ still prefer to regard Friedlander's bacillus in the light of a subordinate rôle (i.e., either as a secondary invader or as a participant in pneumonia metastatic to infection elsewhere). The pertinent literature that has since accumulated is comprised for the most part of individual case reports or at best of small groups of cases. Notable exceptions, however, are the reports of Zander⁵ whose bacteriological data are too limited to be entirely authentic, Belk⁶ whose observations are essentially histological, but excellent, and Solomon⁷ and Bullowa, Chess and Friedman⁸ both of whose publications are detailed, thorough, and convincing.

The writer's interest in this variety of pneumonia dates back to 1923.⁹ Since then a relatively large number of patients has been studied from the bacteriological aspect and it is desirable at this time to place the observations on record. The strains isolated from these patients have been typed according to the classification devised in 1926,¹⁰ as reported to some extent in 1930.¹¹ In addition, this communication will include a discussion of the clinical manifestations, statistics, histology, bacteriology, and a brief word on the therapy of the pneumonia of Friedlander's bacillus. The report will serve the dual purpose of recording personal observations and reviewing related publications of other workers.

* Received for publication February 3, 1941.

From the Department of Ophthalmology, Washington University School of Medicine, Saint Louis, Missouri.

Grants from the Commonwealth Fund of New York aided in part the studies reported herein.

FREQUENCY OF PNEUMONIA DUE TO FRIEDLANDER'S BACILLUS

The pneumonia of Friedlander's bacillus occurs sporadically, although a single report records an outbreak approximating epidemic proportions. Thus, on this one occasion⁵ the infection occurred in a labor camp in Germany afflicting 411 individuals from December 1916 to April 1917. The evidence submitted, however, is bacteriologically scanty and clinically it suggests pneumococcus rather than Friedlander's bacillus as the incriminating organism in a certain proportion of the cases, at least. Usually the disease is encountered in adult life and most frequently during middle age or even later, with a tendency to predominate in males. The predisposing influence of alcoholism on this kind of pneumonia has been stressed by numerous

TABLE I
The Frequency of Friedlander's Bacillus in Human Pneumonia

Investigator	Date	Total number of pneumonias	Incidence of Friedlander's bacillus	
			Numerical	Percentage
Weichselbaum ¹⁷	1886	94	5	5.3
Netter ¹⁸	1892	95	11	11.5
Fraenkel ¹⁹	1908	77	2	2.6
Eyre ²⁰	1910	102	6	5.8
Lord ²¹	1915	192	6	3.1
Avery et al. ²²	1917	480	3	0.6
Cole ²³	1928	183	7	3.3
Habbé ²⁴	1929	131	5	3.8
Heffron and Varley ²⁵	1932	716	7	1.0
Sutliff and Finland ²⁶	1933	1,364	16	1.2
Bhatnagar and Singh ²⁷	1935	100	13	13.0
Bullowa et al. ⁸	1937	4,416	50	1.1
Cecil ²⁸	1937	4,310	33	0.7
Solomon ⁷	1937	5,000	32	0.6
Totals		17,260	196	1.1

authors, as has also trauma, etc., but in the opinion of this writer the cases in which such factors are present are not sufficiently numerous to establish a causal relationship. The writer has never seen an example of this pulmonary disease in infants or children, and the scarcity of references in the literature illustrates clearly its extreme rarity in the lower age groups.¹²⁻¹⁶

A study of the statistics available in the literature indicates that Friedlander's bacillus is responsible for only a small proportion of the total pneumonias. While it is obviously unnecessary to collect all the data bearing on this subject, since it is desirable merely to point out a principle, statistics have been collected from several selected sources in order to convey a general idea of its frequency. Thus, it will be seen from the material assembled in table 1 that varying with the different authors selected, Friedlander's bacillus causes from 0.6 per cent to 13 per cent of all the pneumonias. If, however, all the figures are combined, the composite statistics reveal that of 17,260

pneumonias totaled, 196 were ascribed to Friedlander's bacillus or, stated in another way, this organism occurs in pneumonia in a frequency of roughly one in 100, admittedly a low proportion

FATALITY OF THE PNEUMONIA OF FRIEDLANDER'S BACILLUS

The low incidence of pneumonia associated with Friedlander's bacillus is more than compensated for by its extremely high mortality, so that while the infection is infrequent, it must be considered as serious. In order to display at a glance the fatality of the disease, statistics have been collected and summarized in table 2. While the data thus assembled do not include

TABLE II
Collected Statistics on the Mortality of the Pneumonia of Friedlander's Bacillus

Investigator	Date	Number of		Percentage mortality
		Total cases	Fatal cases	
Kokawa ²⁹	1904	9	9	100
Stulhern ³⁰	1904	10	7	70
Apelt ³¹	1908	10	8	80
Lord ²¹	1915	6	6	100
Sisson and Thompson ³²	1915	4	3	75
Zander ⁵	1919	411	114	28
Belk ⁶	1926	18	18	100
Cole ²³	1928	7	5	71
Kornbloom ³³	1928	4	1	25
Kliewe ¹⁴	1930	11	2	18
Olcott ³⁴	1933	6	6	100
Bhatnagar and Singh ²⁷	1935	13	12	92
Bullowa et al ⁸	1937	39	32	82
Solomon ⁷	1937	32	31	97
Present Report		55	45	82
Miscellaneous single cases ^{12-16 35}		18	15	83
Totals		653	314	48
Totals corrected for Zander's cases (see text)		242	200	82

all possible references bearing on the subject, they nevertheless suffice to indicate clearly the severity of the disease. Analysis reveals that the mortality has been reported as varying from 18 per cent to 100 per cent. The three examples of low fatality can be explained on the following grounds: the infections observed by Kliewe¹⁴ were in children whose susceptibility, judged by incidence, at least, is extremely low, those reported by Kornbloom³³ represent an example of unfortunate sampling, because the three surviving patients progressed from the more acute to the chronic stage of the disease, a less common termination of this form of pneumonia, as will be described below, while the etiology of Zander's cases is not entirely clear, as already explained. In any case accepting these three references on their face value, the collected statistics indicate a total of 653 pneumonias due

to Friedlander's bacillus, and of these 314 were fatal, giving a composite mortality of 48 per cent. If, however, correction is allowed for the numbers submitted by Zander,⁵ the mortality rate rises considerably higher to 82 per cent. Thus it is obvious that the fatality of Friedlander pneumonia is three to four times that seen in pneumococcal pneumonia when untreated with specific antiserum or sulfonamide drugs.

CLINICAL MANIFESTATIONS OF THE PNEUMONIA OF FRIEDLANDER'S BACILLUS

The clinical manifestations of this condition have been described by a number of workers^{1, 5, 7, 8, 21, 30, 31, 32}. Nevertheless, it seems desirable to consolidate existing information with personal observations in a brief running account. The clinical classification of Friedlander pneumonia falls conveniently into three variations—lobular, lobar, and chronic. The most frequent occurrence is an acute, abrupt onset, usually with chill, sharp pain, cough, and fever of variable intensity, but more frequently low (102° F or less). Sputum is usually plentiful, blood-tinged, or rusty, and highly tenacious, its mucoid character together with an excess of blood, often gives to sputa the appearance of reddened tapioca. This is considered as typical of Friedlander's bacillus, but the writer finds no consistent difference between sputa from pneumonia of Friedlander's bacillus and that due to the pneumococcus.

The lobular or bronchopneumonic variety is apparently the least frequent of the pneumonias associated with Friedlander's bacillus. The lesions in this type are essentially scattered and lobular. It may occur purely as bronchopneumonia or conjointly with the lobar form. The most common of the varieties of infection appears to be the lobar, or what some authors prefer to call the pseudolobar form. The consolidation shows great variation anatomically, from localization in a single area in a single lobe to extension throughout one or more lobes and even to involvement of the second lung. Despite numerous attempts to differentiate the lobar pneumonia of Friedlander's bacillus from that of pneumococcus, the writer feels that the clinical similarity between the two is remarkably great, and that usually, the differentiation comes in the nature of a surprise from the laboratory report on the bacteriology of the sputum or blood.

The chronic form of Friedlander pneumonia occurs either as such from the beginning or as a sequel to the acute disease. The former variety is the more common and its onset is slow and insidious, while in the latter, it is initiated in relatively rapid time (five to ten days) by changes in the lung tissue consisting of necrosis and abscess formation, sloughing and cavitation and finally if healing sets in, fibrosis. Thus an occasional patient recovering from the acute phase may pass transitionally into a "chronic pneumonia." Irrespective of its origin, however, the chronic condition eventually becomes clinically indistinguishable, and is characterized as an

exacerbative condition complicated by bronchiectasis and strongly resembling pulmonary tuberculosis. Frequently the continuous absence of acid-fast organisms in the sputum is the first suggestion of Friedlander infection. This form of infection first pointed out by Apelt³¹ was studied with great care by Belk,⁶ who particularly emphasized its similarity to tuberculous infection, as others have since agreed^{35 c, f, h, i, 37}. In this condition the patient may survive indefinitely without great inconvenience or discomfort, as illustrated especially well by the patients described in Collins' ³⁷ report.

In general the disease is relatively short, the duration averaging close to a week. Recovery may be by lysis or crisis, the former apparently predominating. The presence of bacteremia shows great variations, depending upon the different investigators. Thus, of the more recent workers, Cole²³ obtained positive cultures in three of seven patients, Olcott³⁴ in four of six, Bhatnagar and Singh²⁷ in three of 13, Collins³⁷ in one of four; Bullowa, Chess and Friedman⁸ in 27 of 41, and Solomon⁷ in 19 of 27. This makes a combined total of 57 out of 98 patients (ca. 60 per cent) having bacteremia. Our own experience reveals that approximately half the patients whose blood is cultured ante mortem have bacteremia. Yet at postmortem examination, the large majority of patients will show the organism in blood cultured from the heart, indicating at least an agonal, if not postmortem invasion of the organism into the circulation. Another interesting observation clinically is that the severity of the infection is not necessarily reflected in the clinical condition, the patient frequently appearing in relatively good condition until shortly before death.

It is of further interest that extension of the infection to other organs or tissues is more or less infrequent. One of the patients observed in this series showed meningeal signs, and the spinal fluid was purulent and contained the same organism (Type A) as previously isolated from the sputum. Solomon⁷ reports three similar examples in his group of cases.

The blood counts as a rule tend toward a leukopenia, although exceptions are encountered. The shift in white cells is toward the mononuclear elements (lymphocytes and monocytes) at the expense of the polymorphonuclear cells. Sharp decreases in the white cells are usually of grave import. Except for an occasional secondary anemia, the red cells appear to be unaffected.

Roentgenographically, the pneumonia of Friedlander's bacillus has been the object of a special study by several workers^{22, 25 c, f, 28}. Kornbloom³³ describes the disease by this method as a progression of four stages: bronchopneumonia, pseudolobar pneumonia, multiple abscess and cavity formation, and finally healing and fibrosis. However, the consensus of opinion appears to be that in the acute lobar form, roentgenograms are difficult to distinguish from those taken during pneumococcal pneumonia, whereas in the chronic type of infection when cavitation has set in, its distinction from tuberculous

disease is not a simple matter, although the cavity walls appear to be particularly thin *

HISTOLOGY OF THE PNEUMONIA OF FRIEDLANDER'S BACILLUS

The histological changes in the lung due to Friedlander's bacillus are more characteristic of the organism than are the clinical manifestations. Histological discrepancies are found in the literature, apparently due to the fact that the descriptions given are based on single cases, which frequently reveal predominantly one or another variation of the infection at the expense of the general and more commonly encountered changes. A number of reports, however, contain accurate descriptions ^{1, 6, 20, 30, 31 12, 34}. As in the case of the clinical manifestations discussed above, it seems profitable to give a composite picture of Friedlander pneumonia as reported by others and as seen in some of the patients observed in this study. The infected lung is usually voluminous, heavy and consolidated. The cut surface while granular or uniform, is covered with a tenacious exudate which scrapes off on the surface of a knife as a viscous mixture of blood and pus. The distribution of the lesions may be lobular, lobal or both and may sometimes represent a confluence of separate areas of pneumonia. The tissue is for the most part congested and edematous, with the surrounding bronchial glands often swollen and hyperemic. The tissue may be soft, frequently revealing areas of necrosis with beginning or advanced cavitation. Frequently the latter changes are visible grossly, but when undetected by the unaided eye, they are usually to be seen microscopically, so that this progression of tissue destruction constitutes one of the chief distinctions from pneumococcal pneumonia. When infection involves more than one lobe, the pleura of the interlobar septa become adherent and always thickened. Microscopically, the alveoli are greatly distended and filled with an exudate consisting of varying amounts of fibrin, red blood cells, mononuclear, polynuclear and epithelial cells. The alveolar walls are thin, sometimes even completely destroyed, the capillaries are congested, and the pleura may be thickened and edematous. The organism apparently grows more or less unrestrainedly, so that it is found with comparative ease under the microscope both intra- and extracellularly. The greater part of the phagocytosis is apparently taken over by monocytes. There are obviously variations and exceptions from the picture described, so that the description given must be regarded as conforming to that seen most generally.

* It perhaps goes without saying that just as streptococcus and pneumococcus may become secondarily responsible for a pulmonary condition superimposed on preëxisting respiratory infection (e.g. influenza), so also Friedlander's bacillus is occasionally encountered as the chief agent in pneumonia successive to previous disease. Since the "secondary" pneumonia is similar to the "primary" pneumonia, there is little reason for repeating descriptions.

HISTORIES ILLUSTRATING FRIEDLANDER PNEUMONIA

In order to illustrate the general comments made on the clinical, roentgenological, and histological manifestations of Friedlander pneumonia, the histories of two patients are summarized as typical examples *

Case 1 Patient F G was a white male aged 50 years Until the day of admission, the patient had been in good health On that day, he complained of chills and fever, productive cough with blood-streaked sputum, and pain in the chest, all of which appeared abruptly and more or less simultaneously On physical examination, the patient was found to be acutely ill, with a fever of 104° F, and with signs of consolidation over the right upper chest A clinical diagnosis of lobar pneumonia was made and accordingly 120 grains of sulfanilamide were prescribed daily The clinical condition became progressively worse and the patient died on the fifth day of illness In the meantime, roentgenograms revealed a homogeneous density over the right upper lobe, without sign of abscess or cavitation Laboratory examinations disclosed the white blood cells reaching 9,500 per cu mm with 60 per cent polymorphonuclear cells, 30 per cent lymphocytes, and 10 per cent monocytes Blood cultures were sterile, while the sputum contained a predominance of Friedlander bacilli At post mortem, the right upper and lower lobes were covered with a fibrinopurulent exudate and the lung weighed three times more than the left lung (unaffected) The infected lung was almost completely consolidated, and the gross and microscopical diagnosis of lobar pneumonia was justified Bacteriological studies at this time revealed pure cultures of Friedlander's bacillus from the consolidated lung and the exudate

Case 2 Patient A G was a white male, aged 56 years, apparently normal until three months preceding admission to the hospital At this time, he complained of a productive cough, with sputum which was not blood-streaked There was pain in the right lower chest anteriorly, shortness of breath, progressive weakness, and loss in weight of eight pounds Physical examination revealed fever (100.2° F), persistent cough, signs of consolidation over the right lower chest, and clubbing of the fingers A clinical diagnosis was made of bronchiogenic carcinoma Roentgenograms disclosed a homogeneous density over the entire right upper lobe and probably involving a portion of the middle lobe except for an area of radiolucency along the periphery from the clavicle to the fifth interspace On lateral view the radiolucent areas suggested cavities Further roentgen-ray study was recommended because of the difficulty of differentiating between bronchiogenic carcinoma and pulmonary tuberculosis The patient failed rapidly and died on the fifth day following admission Because of the mistaken diagnosis, no laboratory examinations were made At post mortem, the true nature of the disease revealed itself as a chronic suppurative pneumonitis with extensive abscess formation and multiple cavitation Cultures from the lung justified the postmortem diagnosis of chronic Friedländer infection

Figures 1 and 2 are submitted as supplementary to the histories briefly reviewed above

* The clinical histories, roentgenograms and histological sections were obtained from the Philadelphia General Hospital where the writer began his studies on Friedlander's bacillus It is a pleasure to acknowledge the assistance received from the staff, particularly, Drs P H Clark, Harrison F Flippin, S Brandt Rose, and the late Robert G Torrey

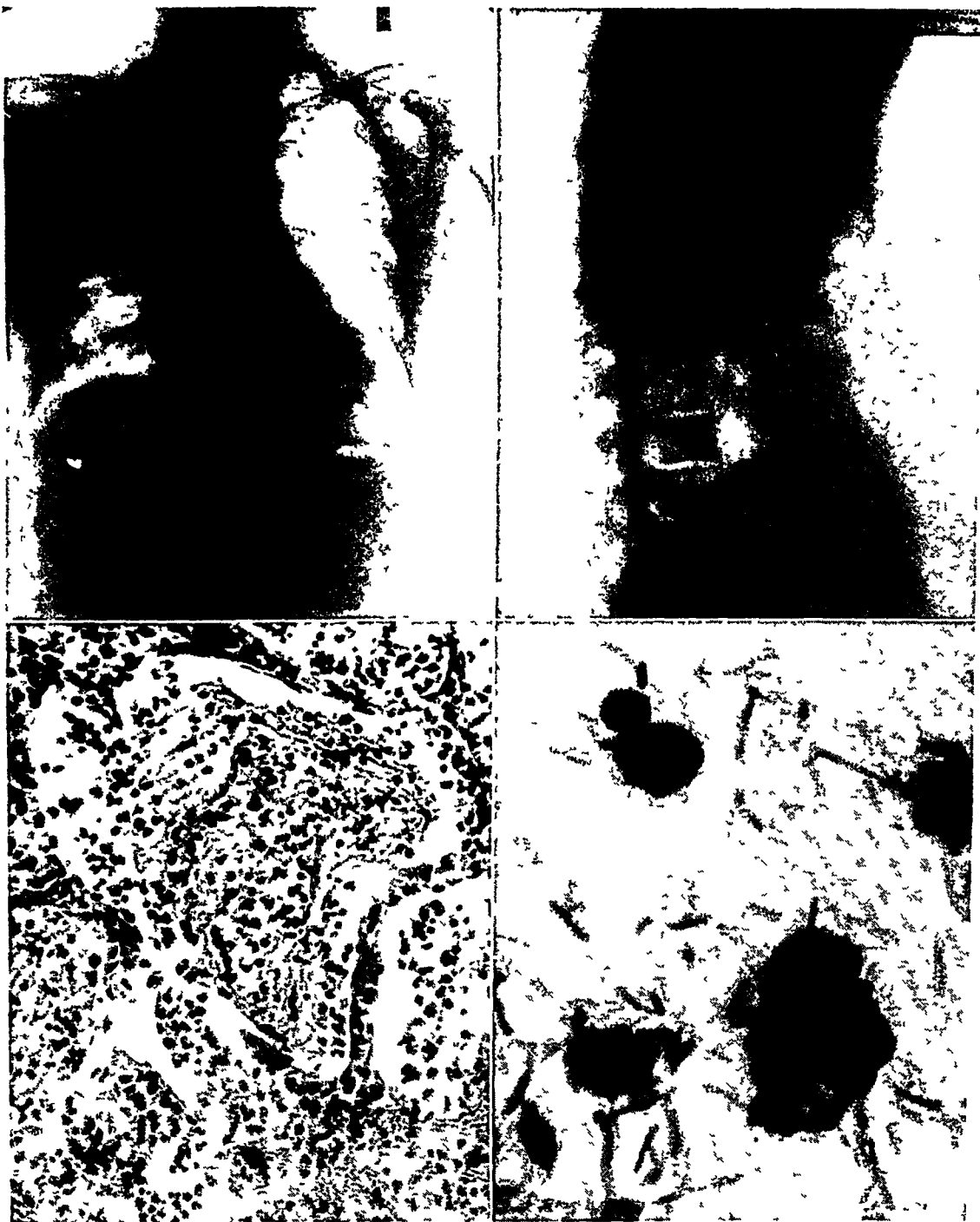


FIG 1 Illustrations to supplement history of patient F G

Upper left Roentgen-ray photograph of chest, anterior view Note homogeneous density over right upper lobe, characteristic of lobar pneumonia

Upper right Roentgen-ray photograph of chest, lateral view Findings are similar to those of anterior view

Lower left Section through consolidated area of lung Note exudate in alveolus, consisting of fibrin, polymorphonuclear and red blood cells and monocytes

Lower right Higher magnification of same section to demonstrate Friedlander bacilli in situ Note monocyte upper left

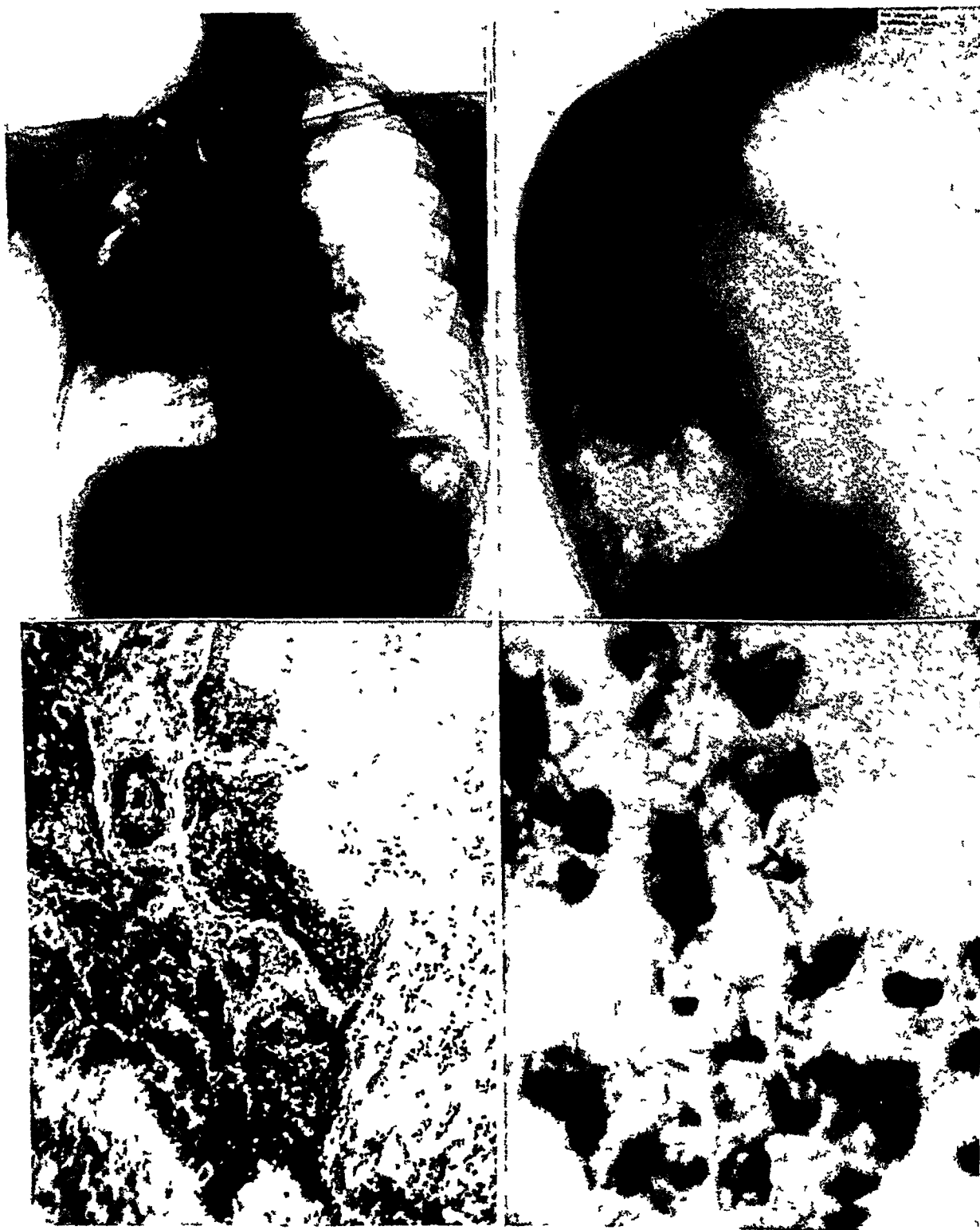


FIG 2 Illustrations to supplement history of patient A G

Upper left Roentgen-ray photograph of chest, anterior view Note homogeneous density over right upper lobe and area of radiolucency

Upper right Roentgen-ray photograph of chest, lateral view Note areas of comparative radiolucency, suggestive of cavities

Lower left Section through consolidated area of lung Note particularly abscess in lower left and cavity along right with formation of wall of fibrin

Lower right Higher magnification of same section to demonstrate Friedlander bacilli in situ

TYPES OF FRIEDLANDER'S BACILLUS AND THEIR RELATION TO PNEUMONIA

That there are several types of Friedlander's bacillus is now generally accepted, and there is reason for believing that Type A is by far the most frequently encountered in pneumonic disease. The detection of types is simple and three satisfactory sources are available for the purpose, of which the most commonly utilized is the sputum. Gram stains usually give the first intimation of the presence of Friedlander's bacillus, the Gram negative organism not only being in typical arrangement, but even exhibiting actual or suggestive capsules on numerous occasions. The type of the organisms may be determined from direct culture of the sputum, peritoneal washings from mice inoculated with the sputum, or preferably by the "quellung" reaction as adopted bodily from pneumococcal typing. Blood is the second source for

TABLE III

Incidence of the Different Immunological Types of Friedlander's Bacillus in Human Pneumonia

Types	Number of strains	Percentage incidence
A	70	64
B	15	14
C	8	7
Group X	16	15
Totals	109	100

typing, and when cultivable in such cultures, the organism may be typed directly by agglutination or by the "quellung" reaction. The third source is from the urine. Blake³⁰ was first to demonstrate that the urine of patients with Friedlander pneumonia may be precipitated in homologous antiserum. Later¹⁰ this was shown to occur in the urine of animals infected experimentally. The writer has been able to determine the type of infecting organism by this method on a number of different attempts. To urine both undiluted and diluted progressively to about 1:80, is added 0.2 c.c. of antiserum and 0.3 c.c. of saline. Incubation is carried out as usual and readings are made after two hours and on the following day after standing overnight in the ice chest. The presence of precipitation in such tests indicates free polysaccharide elaborated by the infecting organism and, therefore, it designates the type of Friedlander bacilli in the lung.

Since Friedlander's bacillus may occur with other organisms also capable of causing pneumonia it becomes necessary to determine when it is primary and when secondary. Obviously in the case of positive blood cultures or of specific precipitation in the urine no other proof is needed. In typing from sputum, however, the evidence may not be so definite. While the following is not always conclusive it is nevertheless a good general rule: when pneumococci are present, the higher the number of their types the less chance of their participation in the infection. In the presence of other potentially pathogenic organisms, Types A and B are probably significant, whereas

Type C and Group X organisms are less significant. At rare times cultures are obtained by lung puncture, when the organisms usually grow in pure culture, thus rendering diagnosis reasonably certain.

Since 1926, when the types of Friedlander's bacillus were defined by immunological methods, 109 strains have been collected by the writer as involved in pneumonia, some of the strains coming from blood, others from lungs, and still others from sputa. While it may be possible that the organism in question was not always the primary infecting agent, it has nevertheless been assumed for different reasons that such was actually the case. The typings performed with these strains are summarized in table 3, where it will be seen that 70 strains or 64 per cent were Type A, 15 or 14 per cent were Type B, eight or 7 per cent were Type C, and the remaining 16 or 15 per cent

TABLE IV

Frequency of the Different Immunological Types of Friedlander's Bacillus in Fatal Pneumonia

Types	Total number of cases	Number of fatal cases	Percentage mortality
A	39	35	89
B	7	5	71
C	4	2	50
Group X	5	3	60
Totals	55	45	82

were classified as Group X. The only other typings known to the writer for comparison are those of Bullowa, Chess and Friedman⁸ and Solomon.⁷ The former found that of 41 patients studied, 24 or 58.5 per cent were infected with Type A organisms, whereas the latter, submitting records on only 10 patients of the 32 studied, reported that typings were conducted in seven of the 10 patients and Type A infection was established in all seven.

It may be of interest to illustrate the mortality of Friedlander's pneumonia as related to the type of infecting organism. Unfortunately it was not possible to obtain the complete records on all of the patients whose cultures were typed. Only 55 patients can be analyzed for this purpose as will be seen in table 4. Of the 55, 39 were Type A and 35 or 89 per cent died, seven were Type B and five or 71 per cent died, four were Type C and two or 50 per cent died; and finally, five were Group X, and three or 60 per cent died. Except for Type A, it is felt that the number of patients of the remaining types was too few for accurate statistics. Nevertheless, the summary reveals that 45 of the 55 patients died giving a mortality rate of 82 per cent. In this connection it should be pointed out that in Bullowa, Chess and Friedman's series 20 of 24 Type A patients died (83 per cent), two of two Type B patients died, one of one Type C survived, and six of eight Group X died (75 per cent).

TREATMENT OF THE PNEUMONIA OF FRIEDLANDER'S BACILLUS

Until very recently the treatment of Friedlander pneumonia consisted almost entirely of non-specific therapy, or what is commonly designated as expectant treatment. With the evolution of types and the advent of sulfonamide drugs, it became possible to attempt specific treatment on the one

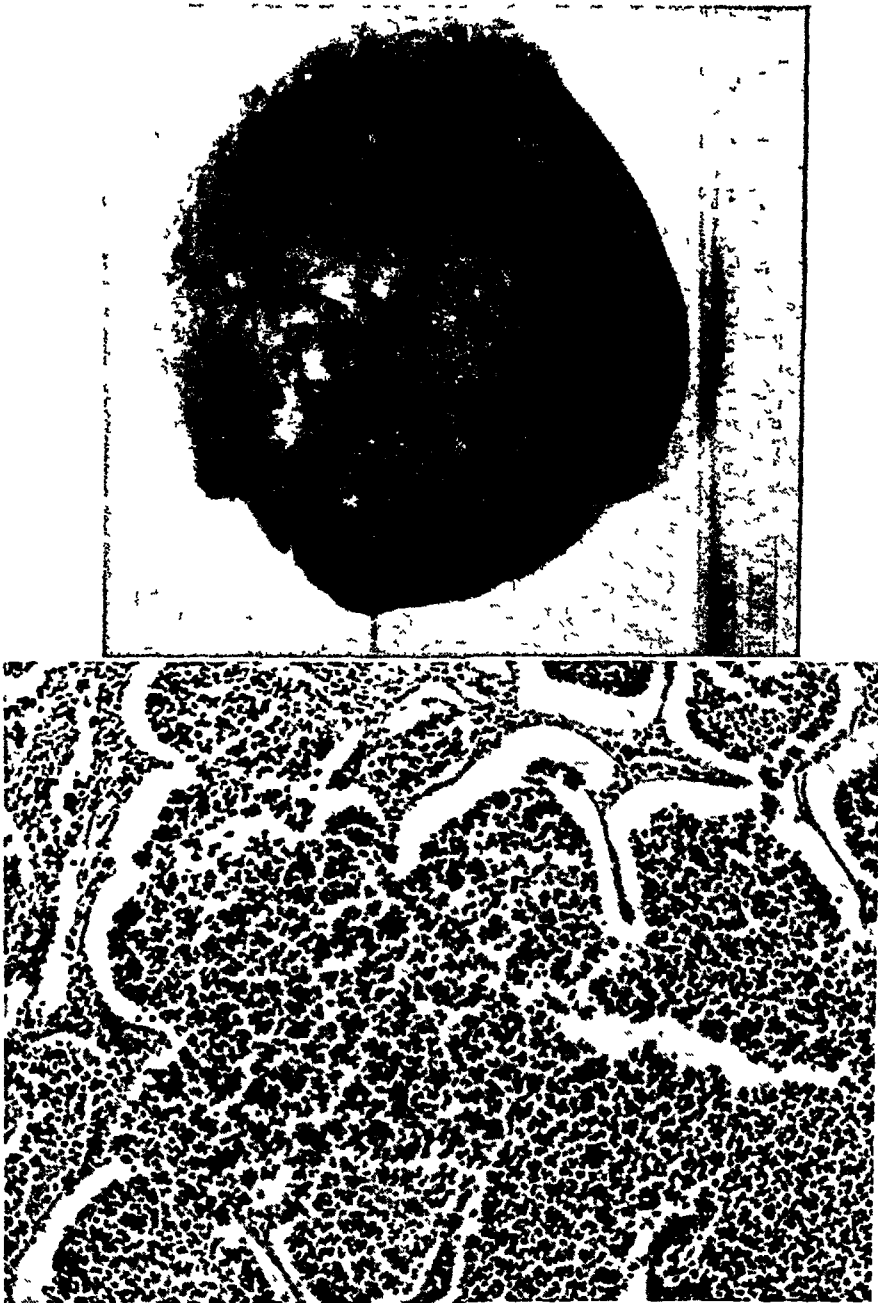


FIG 3 Gross and microscopic changes of the lung

Upper Lung at post mortem, exemplifying voluminous, heavy, and consolidated appearance
Lower Section through infected area to illustrate large collection of polymorphonuclear cells with some monocytes, and degeneration of alveolar walls

hand with antiserum and on the other with chemotherapy. This writer has seen three patients treated with antiserum, all suffering from fatal Type A infection. In each instance, the patients were well along in the course of the disease and did not live long enough for adequate treatment: one received 43 c c of serum, one 38 c c, and the third 60 c c. These trials obviously leave the experiment incomplete and unsatisfactory, and they are consequently of little value in appraising the therapeutic influence of antiserum. As far as can be determined, there are only two other examples of serum therapy. Solomon⁷ in 1937 reported the treatment of five patients with Type A infection, all of whom died. It may be significant, however, that four of these patients died within the day the serum was given, and the fifth patient, receiving 280 c c of antiserum, showed a progressive septicemia and died on the third day following specific treatment, or the eighth day of the disease. It seems, therefore, that serum was not given adequate trial in this group of patients. At about the same time, Bullowa, Chess and Friedman⁸ similarly experimented with serum therapy on eight patients, of whom six received homologous serum. All six patients were treated adequately, from early in the disease, and two on the seventh and sixth days of infection. Three of the patients survived and three died. Admittedly the group is small and the results are correspondingly difficult to evaluate.

Treatment with sulfonamide drugs has been observed in eight patients, six with Type A and two with Type B infection. The former were given sulfapyridine, five patients, sulfanilamide, one patient, while the remaining two received sulfathiazole. A blood concentration of the drug was maintained at supposedly sufficiently high level (8 to 14 mg per 100 c c). As far as could be determined no effect was demonstrated on the course of the infection and all eight patients died, even though the treatment was started early (within 24 to 48 hours). Undoubtedly, others must have given the drugs a similar trial (cf patient F G above), even though the results of such treatment are apparently unpublished.*

DISCUSSION

The accumulated evidence indicates quite clearly that the pneumonia of Friedländer's bacillus is a relatively uncommon disease. The same evidence, however, reveals the infection as highly fatal, holding its own in fact with the most severe bacterial diseases known to medicine. The importance of the pneumonia, therefore, resides not in its frequency, but in its mortality. The distribution of the infection among individuals of middle and old age

* Since the present communication was written, Solomon (Jr Am Med Assoc, 1940, cxxv, 1527-1536) has reported his observations on 17 patients with chronic pneumonia due to Friedländer's bacillus. It is interesting in this connection that four patients were treated with sulfapyridine, the pulmonary suppuration continuing and showing with little apparent effect. Another patient with bacteremia was given sulfanilamide, and while he is considered as recovered, he developed lung abscesses. It would seem, therefore, that this experience parallels that of the present writer in that the sulfonamides are of questionable value in this form of infection.

and its extreme rarity in infants and children are interesting and unexplained facts. Certainly, the infrequency of infection in young individuals does not seem to be referable to lack of exposure, if it be permissible to reason by analogy from pneumococcal pneumonia. On the contrary, it may be that in young pulmonary tissue there is some undefined property of general resistance to the organism, just as pneumococcal (lobar) pneumonia, again, is less severe in this age group than in adult life.

Although a number of similarities exist between Friedlander and pneumococcal pneumonia, the essential difference between the two forms is the tissue destruction in the former. Recovery from pneumococcal pneumonia implies a complete restoration of the involved tissue to normal, so much so in fact that no sign of the forerunning condition is detectable by roentgenological or histological examination. In Friedlander pneumonia, on the other hand, the early formation of necrosis, followed by liquefaction, cavitation, and even fibrosis, may well leave permanent testimony of past infection. In contradistinction to the pneumococcus, therefore, Friedlander's bacillus must be considered as possessing marked capacity for tissue destruction.

The high mortality in Friedlander pneumonia stresses the fact that the urgent problem in this infection is therapeutic. Obviously, general care and expectant treatment have proved themselves insufficient. Reliance at the present time appears to be on the sulfonamide compounds and on serum therapy. The results obtained with the drugs leave the writer less sanguine than does the administration of antiserum. The experiments of Bliss, Feinstone, Garrett and Long,⁴¹ which provide the basis for drug treatment, revealed that such compounds did not bring about survival of infected mice but merely delayed death. It must be remembered, however, that prolongation of life, even for several days, is not recovery from infection. In any case, the observations cited above, while admittedly scanty, point in this direction. It is interesting to note that in a recent review of different diseases treated with sulfonamide compounds, Reimann⁴² lists Friedlander pneumonia among the infections in which the drugs are of doubtful value.

The different attempts already described at serum therapy have been too few and inadequate to allow of a fair estimate of its value or potentialities. Experimental studies, however, suggest that in artificial infection at least, antiserum exhibits a considerable degree of protective effectiveness, and *in vitro* tests, such as agglutination, precipitation of specific carbohydrates, and "quellung" reaction, indicate an avid reactivity between antibody and capsular substance. While obviously such experiments do not assure successful treatment (cf. in this connection Type III pneumococcal pneumonia), the implication in the absence of evidence remains one of promise, as perhaps, the trials of Bullowa, Chess and Friedman⁸ intimate.

SUMMARY AND CONCLUSIONS

- 1 The pneumonia of Friedlander's bacillus is an uncommon infection, occurring once in every hundred pneumonias.

2 The mortality of this disease runs high, attaining a rate close to 82 per cent

3 The clinical and histological characteristics of the pneumonia are enumerated and discussed

4 The different types of Friedlander's bacillus are found in pneumonia in the following proportions Type A, 64 per cent, Type B, 14 per cent, Type C, 7 per cent, and Group X, 15 per cent

5 Type A appears to be the most virulent and fatal form of Friedlander infection

6 Possibilities of specific treatment are discussed, with the recommendation that specific antiserum be given experimental trial

REFERENCES

- 1 FRIEDLANDER, C Ueber die Schizomyceten bei der acuten fibrosen Pneumonie, Arch path Anat, 1882, lxxxvii, 319-324
- 2 TALAMON, D Coccus de la pneumonie, Bull Soc anat Paris, 1883, lviii, 475-481
FRAENKEL, A Weitere Beitrage zur Lehre von den Mikroccocen der genuinen fibrosen Pneumonie, Ztschr klin Med, 1886, xi, 437-458
STERNBERG, Y M The pneumoniococcus of Friedlander, Am Jr Med Sci, 1885, xc, 106-123, 435-438
WHITE, B Biology of the pneumococcus, 1938, Commonwealth Fund Division of Publications, New York, p 11 to 19
- 3 WEICHELBAUM, A Ueber die Aetiologie der acuten Lungen- und Rippen-fellentzündungen, Med Jahrb, 1886, i, 483-554
- 4 BAEHR, G, SCHWARTZMAN, G, and GREENSPAN, E B The rôle of *Bacillus Friedlander* in infection, Trans Assoc Am Phys, 1933, xlviii, 353-354
- 5 ZANDER, A Ausgedehnte Endemie von Lungenentzündungen durch Infektion mit Friedlanderschen Pneumobazillen unter Zivilarbeitern, Deutsch med Wchnschr, 1919, xlv, 1180-1181
- 6 BELK, W P Pulmonary infections by Friedlander's bacillus, Jr Infect Dis, 1926, xxviii, 115-126
- 7 SOLOMON, S Primary Friedlander pneumonia, Jr Am Med Assoc, 1937, cviii, 936-947
- 8 BULLOWA, J G M, CHAFFS, J and FRIDMAN, N B Pneumonia due to *Bacillus Friedlander*, Arch Int Med, 1937 lx, 735-752
- 9 SMALL, J C, and JULIANELLE, L A Biologic and serologic studies of *Bacillus mucosus* group, Jr Infect Dis, 1923, xxii, 456-470
- 10 JULIANELLE, L A A biological classification of *Encapsulatus pneumoniae* (Friedländer's bacillus), Jr Exper Med, 1926, xlv, 113-128
- 11 JULIANELLE, L A The distribution of Friedländer's bacilli of different types, Jr Exper Med, 1930, lxi, 539-545
- 12 ETIENNE, G Le pneumobacille de Friedlander son role en pathologie, Arch med exper, 1895 vii, 124-157
- 13 COMBA, C Setticemia da bacillo del Friedlander in un neonato, Arch Biol, 1896, i, 112-128
- 14 KLEINF, H Epidemiologische und biologische Studien über den *B pneumonia* Friedländer und verwandte Arten, Cent Bakt I O 1930, cxvi, 92-101
- 15 FERGUSON, J A, and TOWER, A A Pneumonia in infants due to *Bacillus mucosus-capsulatus* Am Jr Dis Child, 1933, xli, 59-68
- 16 DUNN, C H, and HAMMOND, J. A case of Friedlander's pneumonia with recovery, Interstate Med Jr 1915, xii, 1133-1135
- 17 WEICHELBAUM, A See reference 1

- 18 NITIER Etude bacteriologique de la bronchopneumonie, Arch med exper, 1892, iv, 28-65
- 19 FRANKF, E. Personal communication to Apelt ¹¹
- 20 EYRE, J The bacteriology of broncho-pneumonia A statistical analysis, Jt Path and Bact, 1910, xiv, 160-163
- 21 LORD, F T Diseases of the bronchi, lungs, and pleura, 1915, Lea and Febiger, Philadelphia, p 234
- 22 AVERY, O T, CHICKERING, H T, COLE, C, and DOCHTIZ, A R Acute lobar pneumonia Prevention and serum treatment Monographs of the Rockefeller Institute for Medical Research, No 7 1917
- 23 COLE, R Acute pulmonary infections, in De Lamar lectures, 1927-28, Williams and Wilkins Co, Baltimore
- 24 HÄUBL, K Zur Bakteriologie bei Lungenentzündungen des Menschen, Deutsch med Wchnschr, 1929, lv, 1506-1508
- 25 HEFFRON, R, and VARLEY, F M A study of lobar pneumonia in Massachusetts methods and results of pneumococcus type determinations, 1931-1932, Am Jr Pub Health, 1932, xxii, 1230-1248
- 26 SUTLIFF, W D, and FINLAND, M The significance of the newly classified types in disease, types IV to XX inclusive, Jr Am Med Assoc, 1933, ci, 1289-1294
- 27 BHATTNAGAR, S S, and SINGH, K Bacteriological studies in acute lobar pneumonia due to *B pneumoniae* Friedlander, Indian Jr Med Res, 1935, xxiii, 337-345
- 28 CECIL, R L Text-book of medicine, 1937, W B Saunders, Philadelphia, p 107
- 29 KOKAWA, I Zur pathologischen Anatomie der Kapselbazillen Pneumoniae, Deutsch Arch klin Med, 1914, lxxv, 39-74
- 30 STULHFRN, V R Ueber die Bedeutung des *Bacillus pneumoniae* Friedlander als Erreger von Pneumonie, Centralbl f Bakt I, O, 1904, xxxvi, 493-505
- 31 APELT, F Ueber die durch den *Bacillus pneumoniae* Friedlander hervorgerufene Pneumonie, München med Wchnschr, 1908, lv, 833-837
- 32 Sisson, W P, and THOMPSON, C B Friedlander bacillus pneumonia with a report of cases, Am Jr Med Sci, 1915, cl, 713-727
- 33 KORNBLUM, K Roentgen-ray diagnosis of pulmonary infections with Friedlander bacillus, Am Jr Roentgen, 1928, xiv, 512-521
- 34 OLCOTT, C T Pneumonia due to Friedlander's bacillus, Arch Path, 1933, xvi, 470-479
- 35 (a) BECO, L Recherches sur la frequence de septicémies au cours des infections pulmonaires, Rev med, 1899, xix, 461-479
- (b) SMITH, W H A case of lobular pneumonia due to *Bacillus mucosus-capsulatus*, Jr Boston Soc Med Sci, 1897, ii, 174-179
- (c) THIROLOIX, M Pneumonie due au bacille de Friedlander, Bull Soc anat Paris, 1897, lxxii, 152-154
- (d) PHILIPPI, E Ein Fall von krupposer Pneumonie und Sepsis, hervorgerufen durch den Pneumobacillus Friedlander, München med Wchnschr, 1902, xlix, 1884
- (e) WESTERMARK, N Ein Tuberkulose vertäuschender Fall von Friedlander's Pneumonie mit lange sich hinziehendem Verlauf, Acta radiol, 1926, vii, 626-631
- (f) BRULÉ, M, HUGUENIN, R, and GILBERT-DREYFUSS Pneumopathie chronique a bacilles de Friedlander, Bull et mem Soc med d hôp d Paris, 1927, li, 1370-1378
- (g) ABRAMI, P, and WORMS, R Septicemie à pneumobacilles de Friedlander avec localization pulmonaire, Ibid, 1930, liv, 479-486
- (h) SCHLAPPER, K Ueber Friedlander-Pneumonien, Beitr z Klin d Tuberk, 1931, lxxviii, 741-749
- (i) SWEANY, H C, STADNICHENKO, A, and HENRICHSEN, K J Multiple pulmonary abscesses simulating tuberculosis caused by the Friedlander bacillus, Arch Int Med, 1931, xlvii, 565-582
- (j) BENSLEY, E H A case of Friedlander's pneumonia, Canad Med Assoc Jr, 1932, xxvi, 681-684

- (k) FREMMEL, F, HENRICHSEN, K J, and SWEANY, H C Pneumonia from Friedlander's bacillus, ANN INT MED, 1932, v, 886-894
- (l) STOICHITA, N N, and JONNESCO, D Abscès au poumon et septicémie à pneumobacilles de Friedlander, Arch méd-chir d l'app respir, 1933, viii, 534-541
- 36 HEFFRON, R Pneumonia, Commonwealth Fund Division of Publications, New York, 1939, p 5-8
- REIMANN, H A . Section on pneumonia in Cyclopedia of medicine, Edited by G M PERSOL, 1939, F A Davis Co, Philadelphia
- 37 COLLINS, L H, JR Chronic pulmonary infection due to the Friedlander bacillus Further observations, Arch Int Med, 1936, lvi, 234-249
- 38 HART, A L The postpneumonic lung A critical review, Am Jr Roentgenol, 1931, xxvi, 371-396
- 39 BLAKE, F G Antigen-antibody balance in lobar pneumonia, Arch Int Med, 1918, xxi, 779-790
- 40 JULIANELLE, L A Immunological relationships of cell constituents of *Encapsulatus pneumoniae* (Friedlander's bacillus), Jr Exper Med, 1926, xlv, 735-751
- 41 BLISS, E A, FEINSTONE, W H, GARRETT, A W, and LONG, P H Sulfapyridine and sulfanilamide in experimental pneumococcal, meningococcal, Welch bacillary, and Friedlander's bacillary infections in mice, Proc Soc Experi Biol and Med, 1939, xl, 619-621
- 42 REIMANN, H A Infectious diseases A review of significant publications in 1939-1940, Arch Int Med, 1940, lxxvi, 478-525

WEIL'S DISEASE; REPORT OF THREE CASES, INCLUDING THE MORBID ANATOMY OF ONE CASE, AND A BRIEF REVIEW OF THE PERTI- NENT LITERATURE¹

By JOEL J WHITE, M D , F A C P , and JOHN V PREVOST, M D ,
Philadelphia, Pennsylvania

IN 1886, H A Weil¹ described a syndrome characterized by the sudden onset of prostration, fever, myalgia, jaundice, hemorrhagic tendencies and renal damage which, today, is known by his name Inada and Ido² discovered the spirochete in the liver of a guinea pig, inoculated with the blood of a patient suffering from the disease in 1915, and believed it to be the causative agent They succeeded in isolating and culturing the organism and named it *Spirocheta icterohemorrhagica* The following year Inada³ and a group of Japanese reported extensively on the etiology and mode of infection of this disease In 1918, Hideyo Noguchi⁴ classified the organism under the genus *Leptospira*, as he had proposed in a previous report,⁵ retaining the nomenclature *icterohemorrhagica* set forth by Inada² Other synonyms for the disease include infectious jaundice, spirochetal jaundice, spirochetosis icterohemorrhagica, spirochetosis and recently the term leptospirosis⁶ has been used to include the mild type of Weil's disease, most frequently seen in the United States

The disease has a world-wide distribution as would be expected since the *Leptospira* is an ubiquitous organism⁷ However, relatively few cases have been reported in this country probably because the disease remains unrecognized in the majority of cases In 1922, Wadsworth⁸ reported the first proved case on the North American continent Gaines and Johnson reviewed the literature on the subject and contributed seven cases from Colorado in 1937 They were able to collect 13 cases, published prior to their cases, reported from the states of New York,¹⁰ Virginia,¹¹ District of Columbia,¹² Pennsylvania,¹³ California¹⁴ and Massachusetts¹⁵ Since 1937 we have succeeded in finding four cases reported from New York¹⁶ and Texas,¹⁷ making a total to date of 24 cases reported in the United States An epidemic of this disease was the subject of a preliminary report from Detroit, Michigan¹⁸, and personal correspondence with the Pennsylvania State Board of Health¹⁹ revealed four separate outbreaks of a mild type of Weil's disease in the mining areas of this state during the past year Recent reports from all parts of the world are too numerous to include

* Received for publication January 31, 1940

From the Medical Service of U S Naval Hospital, Philadelphia, Pa

In this paper we wish to report three proved cases of Weil's disease, including the morbid anatomy of one case, briefly review the subject, suggest that a method, previously described for obtaining adequate darkfield preparations from gonorrheal discharges, may be applied to routine darkfields on jaundiced patients, and discuss some of the interesting aspects of our cases as compared to other reported cases

CASE REPORTS

Case 1 B F was a married, white, Hebrew male, aged 39, resident of Philadelphia and a laborer on a W P A quarry project until October 1, 1937 on which date he experienced an acute onset of chills, fever and severe prostration. The following day he noted a yellow discoloration of his skin and eyes, began to have mild nausea, epigastric discomfort, general malaise, anorexia and myalgia. During the next few days, the jaundice increased and was accompanied by generalized pruritus, his urine became dark in color and his stools acholic. The past medical and family history was negative. He was admitted to the Medical Service as an ambulatory patient October 10, 1937 and was recorded as being a well nourished, slightly icteric, middle aged male weighing 154 pounds. Slight tenderness to palpation in the epigastrium, a tender and enlarged liver whose edge extended three inches below the right costal margin and a questionably palpable spleen were the only positive physical findings on admission.

Initial laboratory studies revealed the blood Kahn, sedimentation rate, coagulation time, bleeding time, erythrocyte fragility, total erythrocytes and leukocyte counts, hemoglobin and Schilling differential to be negative or within normal limits. Abnormal findings included urine bilirubin, blood icterus index of 50, blood bilirubin 2 mg per 100 c c and a qualitative Van den Bergh which gave a direct immediate reaction. A gall-bladder drainage was positive for bile pigments, negative for cholesterol crystals, contained a few erythrocytes, leukocytes and bacterial clusters in each of three specimens taken in the routine manner.

During the ensuing days of October, the patient ran a slight elevation of temperature but showed some clinical improvement. The urine became lighter, the stools darker in color. The icterus index fell to 45, the leukocyte total and differential count remained normal, but erythrocytes and hemoglobin fell gradually to 3,870,000 and 75 per cent respectively. On October 26, darkfield examination of the blood serum was positive for *Leptospira*, while a similar examination of the urine was negative.

Two days later, the patient complained for the first time of a sharp, knife-like pain across the right diaphragm, which lasted five minutes and suggested biliary colic. Following this, he continued to have epigastric distress, and on November 12 a single roentgenogram of the abdomen showed the liver and spleen to be enlarged, the edge of the liver extending down 2 cm below the crest of the ileum, but no shadows suggesting biliary or renal calculi were noted. During the early part of November, the icterus index rose coincidentally with epigastric distress, attaining a level of 75 for the first two weeks. The urine became highly colored and the stools varied in color from dark brown to light yellow at intervals of several days. The leukocyte count rose to 11,100 with a slight shift to left in the Schilling hemogram. On November 25, the patient suffered an attack of upper abdominal pain clinically resembling biliary colic. The patient continued to have attacks of biliary colic, of increasing severity, on each of four succeeding days and the icterus index rose to 150. At this time it was felt that there was some common duct obstruction which required surgical intervention though a positive agglutination test for *Leptospira* was reported from The United States Naval Medical School on this date. On December 1, 1937, a

cholecystogastrostomy was performed through a high right rectus incision. The operative findings were recorded as follows: "Liver enlarged, spleen enlarged three times its normal size. Gall-bladder was distended with about 150 c c of thick, granular, dark red, hemorrhagic material which coagulated upon removal. The head of the pancreas was soft. No stones were palpated in the gall-bladder or biliary ducts." Darkfield examination of the material aspirated from the gall-bladder at operation, was positive for *Leptospira*. The patient responded well to the operation, the icterus index falling to 50, within 10 days. Operative convalescence was entirely uneventful, and during the next three months the patient appeared to be improving, though the icterus index varied between 37 and 86, averaging about 50. On March 22, 1938 daily intramuscular injections of liver extract were initiated and the patient responded shortly thereafter with a gradual rise in erythrocyte and hemoglobin values, while the icterus index progressively decreased, achieving a normal value of 6 on May 18 for the first and only time during his hospitalization. The patient felt greatly improved and clinically appeared to be well.

Early in June, a sudden unexpected and unexplainable change occurred, the patient began to fail, the erythrocytes and hemoglobin began to decline, the leukocyte count rose with increasing shift to the left, and the icterus index value gradually increased to 25. The end of June found each of these values continuing their respective rise or decline in the same direction, though there was less shift to the left in the Schilling hemogram. On July 2, 1938, the patient began to pass dark red blood by rectum and became edematous. The melena continued during the next four days, when he began to vomit blood as well. During this time, the erythrocyte count reached a level of 750,000 with hemoglobin of 10 per cent, the leukocytes rose to 27,700 and exhibited a shift to the right. The icterus index attained 75. Direct blood transfusions were given on alternate days in amounts of 500, 500, 750 and 750 c c, but the patient failed to respond and expired July 17, 1938 following an illness lasting nine months and 17 days.

A necropsy was performed with the following gross findings. The tissues were bile stained and edematous. Both pleural cavities contained about 200 c c of clear, straw colored fluid, and the lungs were edematous, the right weighing 800 and the left 840 gm. The heart was slightly bile stained, the myocardium pale, and the right ventricle slightly dilated. The abdomen was filled with a greenish ascitic fluid. The gastrointestinal tract was filled with partially digested blood and the entire mucosa was covered with petechial hemorrhages. The stoma of the cholecystogastrostomy was intact and admitted one finger, the gall-bladder was filled with soft blood clots. The common duct was patent. The liver was considerably enlarged, weighing 2,775 gm, dark green in color and rather firm in consistency. On section, the surface suggested marked biliary cirrhosis. An abscess 6 cm in diameter was discovered in the left lobe and distended both the superior and inferior surfaces, on section, it was found to be well encapsulated. Cultures from the abscess yielded *Escherichia coli*. The spleen weighed 300 gm, and appeared normal. The kidneys were pale, edematous and bile stained, the right weighed 190 gm and the left 200 gm.

Microscopic examination of sections from the above organs revealed the following findings. The liver showed an ascending cholangitis with periductal fibrosis and infiltration of round cells about the afferent vein and biliary radicles. The bile ducts in these areas showed proliferation and budding. The liver cells varied in size and bile content, those about the afferent vein contained the most bile. The nuclei were vesicular and varied in size and number, often two or three being present in a single cell. A small amount of fatty infiltration was observed about an occasional afferent vein. Several miliary abscesses, as well as areas of focal necrosis, were noted. The latter had a central and mid-zonal distribution. What was thought to be an abscess was an extensive area of necrosis well encapsulated by fibrous tissue, and adjacent

pressure necrosis of liver cells Extensive fibrosis in this locality was of the nodular type

Except for an occasional group of necrotic epithelial cells, the surface of the gall-bladder mucosa was completely eroded. The surface was covered with a necrotic, hemorrhagic, fibrinous exudate which contained relatively few leukocytes. The lamina propria was swollen and tightly packed with eosinophiles and wandering phagocytes. The lower layers had undergone extensive fibrosis and hyalinization. The muscle cells showed focal degeneration, selective vacuolization and hyalinization.

The tubules of the kidneys were dilated and contained varying amounts of albumin. The tubular cells were swollen, necrotic, and occasionally contained globules of bile. The glomeruli appeared quite normal, but were often surrounded by interstitial fibrosis and edema.

The sheathed arteries of the spleen were unduly prominent. No Malpighian corpuscles persisted, but occasional minute collections of lymphocytes were noted. The entire organ was involved in a diffuse fibrosis. The sinusoids were packed with erythrocytes, round cells and hemosiderin bearing phagocytes.

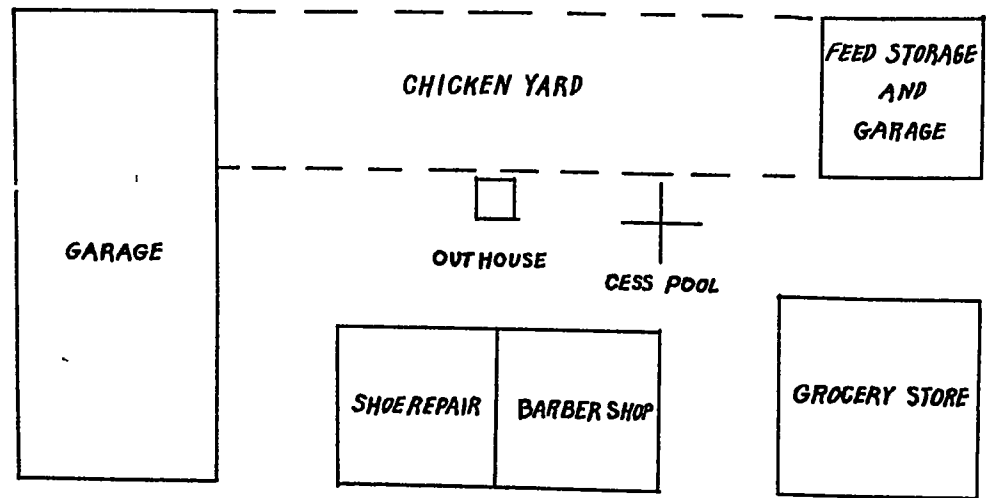


FIG. 1 Diagrammatic illustration of the area in Williamstown, New Jersey from which the rats, studied in case 2, were obtained. The garage in which the patient worked is at the left.

In the lymph nodes the stroma was very edematous, and nothing remained except a delicate reticulum in which small deep staining lymphocytes were sparsely enmeshed. No primary or secondary follicles existed. The collecting sinusoids contained considerable numbers of hemosiderin bearing phagocytes.

The pancreas exhibited slight periductal fibrosis. Several small capillary hemorrhages in the islets of Langerhans were observed.

The heart muscle was edematous and the cell striations indistinct. Occasional selective vacuolization of individual cells was noted.

The lungs were edematous and showed a terminal patchy bronchopneumonia.

The adrenals showed lipid depletion but no evidence of hemorrhage.

Unfortunately sections from the gastrointestinal tract were not taken.

Case 2 P W S was a married, white male, aged 46, who was a resident of Williamstown, New Jersey (approximately 20 miles from Philadelphia). This town had a piped water supply but no sewerage system, most dwellings and places of business used covered cesspools or outhouses. The patient worked at a garage situated in a business block with four other buildings, as shown in figure 1. Numerous rats were seen in all areas and buildings situated within the block.

For several weeks prior to the patient's illness there had been heavy rains in that vicinity and water had accumulated in the cellars of the buildings. The garage had a heater pit which the patient was required to bail out almost daily, at a time when he had several abrasions on his hands, which were in evidence on admission. He noted that the one on his thumb was especially indolent in healing.

On March 13, 1939, he experienced anorexia, weakness and malaise and the following day, had a rather sudden onset of chills, slight fever and moderate prostration. Two days later his skin became yellow and his urine dark in color. During the next few days his symptoms abated but, on March 20, the fever and prostration returned, the jaundice increased, the urine remained dark and his stools became clay colored. He developed a marked pruritus which caused him to scratch himself. These scratches bled freely and purple lumps raised up about the abrasions. Again the fever, prostration and other symptoms receded though the jaundice remained the same. He was admitted as an ambulatory patient to the Medical Service on March 24, 1939. On admission, he had a temperature of 99° F, the skin and sclerae were moderately icteric and there were multiple scratch marks over the whole body with peculiar secondary inflammatory purple areolae about some of the lesions. The left lobe of the liver was barely palpable and not tender. The spleen was not palpable. There were no other positive findings.

Initial laboratory studies included the darkfield examination of the blood serum which was positive for *Leptospira*. The icterus index was 35, the qualitative Van den Bergh biphasic, urine was positive for urobilin but darkfield negative. The total erythrocyte and leukocyte counts, hemoglobin, Schilling hemogram, erythrocyte fragility test, coagulation and bleeding time were within normal limits. Guinea pig inoculations were made with the patient's blood and with catheterized urine. A specimen of blood was sent to the United States Naval Medical School for agglutination tests. The patient was placed on a high carbohydrate, high vitamin, dietary regime and was allowed to be active about the ward. At no time after admission did his temperature go above 100° F, he felt well and complained only of pruritus. Repeated darkfields on the urine were negative, but a positive result was finally obtained on April 4. The icterus index gradually receded to 6 by April 20, reaching 3 on April 26, rising again to 12 without any new symptoms and finally receding to normal at the time of discharge. The hemorrhagic inflammatory lesions gradually healed. Darkfields on serum from these lesions were negative. Darkfields on blood and urine on May 17 were both negative and the patient was discharged completely well. A follow-up since that time found the man in good health.

The agglutination test taken on March 27 proved to be negative against the strain of *Leptospira* used at the Naval Medical School.

Both the inoculated guinea pigs appeared to be ill on the eighth day and died on the tenth day following the injections. No jaundice was noted in either pig. However, they were light tan in color and it may have been overlooked.

Autopsy findings on the blood injected pig revealed a subcutaneous hemorrhage in the abdominal wall, the lungs were slightly hemorrhagic and there were two extravasations of blood into the superficial cortex of the right kidney. The liver was not grossly abnormal, the gall-bladder was distended with lemon yellow bile. Darkfield examination of the blood serum was positive, but the urine and bile were negative.

Autopsy examination of the urine inoculated pig disclosed "butterfly type" hemorrhages in the lungs, and the gall-bladder was distended with hemorrhagic bile. The liver, spleen and kidneys were not grossly abnormal. Darkfields on the urine were negative. Darkfields on the bile showed an occasional *Leptospira* and those on the blood serum contained 2 to 3 organisms per oil-immersion field. A Fontana stain of the pig's blood serum showed *Leptospira*.

On March 29, 1939, a rat was brought in from the colony about the garage. It had been caught in a trap and had been dead 48 hours. Postmortem examination

showed pulmonary hemorrhages, a yellow, speckled liver, and engorged kidneys. Darkfield examination of a liver emulsion was negative for *Leptospira*. Sections of the lungs, liver and kidneys were made and were stained by Levaditi's method. The cells of the renal tubules contained an occasional *Leptospira*.

On April 17, 1939, a live rat from the colony at Williamstown was obtained. The rat was anesthetized with ethyl chloride, a piece of its tail was cut off, and darkfield preparations were made from the blood. Examination of the preparations showed numerous *Leptospira* which resembled those seen in the patient's blood and in that of the guinea pig. Preparations were being made to make further studies of the rat on the following day. The rat survived the anesthesia and appeared well immediately after the darkfield preparations had been made, but it died that night and was not discovered for some time. Darkfields on the blood, urine and liver emulsions of the dead rat were negative.

Case 3 M O was a healthy, single, dark complexioned white female, aged 19, who was studying art in Philadelphia. She resided in the southern part of the city, where large vacant fields, formerly used as piggeries, surrounded her dwelling place. On several occasions she had seen rats in the kitchen and dining room, but denied direct contact with them. She did recall releasing a mouse from a trap some time prior to her illness and admitted nocturnal barefoot excursions to the kitchen.

On March 19, 1939, she developed anorexia, malaise, moderate prostration, slight chills and fever, which continued for several days. On the fourth day, she began to have a dull pain and tenderness to palpation in the right upper quadrant. These symptoms became more marked. She developed a generalized pruritus and, on March 26, it was noted that her sclerae were yellow. During the next few days, the fever, malaise and prostration abated, but the jaundice increased, an icterus index reading on March 27 being 12. On April 1, the skin was definitely icteric, and she continued to have occasional attacks of right upper quadrant pain. A blood count showed 4,150,000 erythrocytes, 78 per cent hemoglobin and 5,300 leukocytes with a differential of 44 per cent neutrophils of which 36 were segmented and 8 were band forms, 45 per cent lymphocytes and 11 per cent monocytes. The blood sedimentation rate was 15 mm in 60 minutes.

Her urine became very dark and the stools clay colored. She remained ambulatory, but had a return of anorexia and malaise as the jaundice deepened. On April 4, the icterus index was 28, the qualitative Van den Bergh gave a positive biphasic reaction, and the Takata test was positive. A darkfield examination of the blood serum on April 8, disclosed *Leptospira*, while a similar examination of the urine on April 10, was negative. The urine was strongly positive for bilirubin but was otherwise negative. A gall-bladder drainage, on April 17, 1939, contained a small amount of bile pigment and a few erythrocytes, leukocytes and epithelial cells in each of the three routine samples. The icterus index continued to rise and was 75 on April 19. On April 23, she began to run a low grade fever, had nausea, indigestion and a rather irritating cough. She had lost 12 pounds since the beginning of her illness. On April 26, she was admitted to the Medical Service, where physical examination revealed marked jaundice of the skin, sclerae and mucous membranes as the only positive findings. The liver and spleen were not palpable.

The icterus index attained a value of 150 for two readings over a period of seven days, during which time the patient became almost psychotic from the intolerable pruritus and the continual bronchial irritation and cough. On April 4, intramuscular injections of liver extract were initiated, and the patient responded with immediate clinical improvement, the icterus index falling to 100 on April 6 and to 30 on April 9. The cough and pruritus receded with the jaundice and she was discharged on April 20, 1939 convalescent, a follow-up showing complete recovery with a recent normal liver function test.

While under study, this patient had a doubtful positive blood Kahn test, although there is no reason to suspect the possibility of luetic infection

On April 12, two guinea pigs were inoculated with whole blood and with catheterized urine, obtained from the patient under sterile precautions Both pigs appeared to be ill on the seventh day The blood inoculated pig died on the eighth day and the urine inoculated pig died on the tenth day Both pigs showed typical post-mortem changes, with butterfly hemorrhages over the base of the lungs, hemorrhagic bile and congestion of the liver and kidneys Darkfields on the blood of both guinea pigs were positive for *Leptospira*

BACTERIOLOGY, EPIDEMIOLOGY AND IMMUNOLOGY

The *Leptospira* are a genus of spirochetes, so named because of their fine coils, to quote Noguchi's original description "the number of coils is greater in a given length than that of any spirochete hitherto known" Their length is variable from 3 to 40 μ , averaging about 9 μ One or more gentle undulations occur throughout the entire length The ends are sharp, and one or both may be semi-circularly hooked or formed as an eyelet Most characteristic is the highly motile end portion consisting of the last 6 to 8 spirals which seem to flex on the organism Upon darkfield examination, one or both ends appear club-shaped, and the tightly wound coils may appear as chains of coccoid bodies This spirochete is quite active and usually takes an erratic course, with rotation and lashing movements of the extremities The organism may be stained by either Levaditi's or Fontana's method In these preparations the *Leptospira* appear much thicker because of the deposition of silver salts upon their surface Readers who are unfamiliar with the identification of these organisms are referred to the reports of Inada³ and Noguchi⁴ which include numerous microphotographs of darkfield and stained preparations

In the course of our investigations on cases 2 and 3, we found the method described by Friedman,²⁰ for obtaining darkfield preparations of *Treponema pallidum* from gonorrheal discharges, highly advantageous and satisfactory, especially for obtaining blood serum from the dead guinea pigs Briefly, the technic consists of obtaining the specimen in a section of ordinary capillary glass tubing approximately 10 cm in length, such as that used in routine coagulation tests After the specimen has been obtained, the opposite end from which the specimen was taken is sealed in a Bunsen burner The capillary tube is then placed, sealed end downward, in a centrifuge tube and is centrifuged for 5 to 10 minutes It is then removed and it will be found that the sealed end contains the cellular portion of the specimen This is broken off just to the serum side of the line demarcating the clear supernatant fluid from the cellular suspension A bulb from a smallpox vaccination set is placed on the end of the capillary tube, and the clear, supernatant fluid or serum is expressed upon a cover slip, which is then set up in a routine manner This technic was used in the study of the patients, by taking the capillary

specimen from oxalated blood drawn for blood chemistry or for the sedimentation rate. In these preparations we found more *Leptospira* per field than with any other method when both preparations were taken from the same specimen at the same time. We recommend this method for routine darkfield examinations on all jaundiced patients.

Authorities vary as to the difficulty of obtaining cultures of these organisms. The non-pathogenic *Leptospira biflexa* may be cultured on autoclaved suspensions of feces, to which 5 per cent nutrient agar or gelatin may be added.⁷ Noguchi⁸ recommended a medium consisting of rabbit serum one part; normal saline or Ringer's solution, three parts, and 0.5 part rabbit plasma, covered with a thin layer of sterile paraffin oil, for the growth of *Leptospira icterohemorrhagica*. We were unable to obtain positive cultures from our cases on the ordinary blood and ascitic media.

Weil's disease is evidently contracted by infection of the intact or abraded skin from contaminated water.⁹ A group of Japanese workers²¹ also noted that the disease was common in wet mines in which the workers went bare-foot, that it was endemic in regions with neutral or alkaline soil, but was rare or absent in dry mines or regions in which the soil was acid. The water is believed to be contaminated by the urine of wild rats which are frequently found to be infected with *Leptospira icterohemorrhagica* (Blumer). Wild mice are not generally infected since their habitats are not so closely associated with water, but they may transmit the disease.

In California, cases were traced to the handling of dogs suffering from "yellow or Stuttgart's disease". A survey of dogs suffering from the disease showed them to be infected with either *Leptospira canicola* or *Leptospira icterohemorrhagica*.⁶ The disease caused by the former strain of *Leptospira* has been called Canicola fever, runs a much milder course, and is often without jaundice. The transmission of Weil's disease by dogs is an accepted fact, having been proved in several cases. Numerous epidemics and cases have been traced to bathing in swimming pools, ponds or lakes. Jeghers, Houghton and Foley¹⁶ ridicule the possibility of human carriers, but we feel that this is a definite means of contamination.

Infection with Weil's disease confers a definite and lasting immunity which appears to be humoral in character. The antibodies which develop resemble those of a syphilitic infection to some extent since the Wassermann reaction may become positive during an attack of infectious jaundice.²² As criteria of infection, serological tests are not reliable because of the antigenic variation of the many strains of *Leptospira*. Antibodies have been demonstrated in the blood as early as the fifth day, but they reach their maximum development about the twenty-fifth day of the disease. With their development, the spirochetes disappear from the blood and are found in the urine on the sixth or seventh day, persisting there as long as 40 to 60 days, reaching a peak at about 25 days.

PATHOLOGY

The morbid anatomy is mainly concerned with the effect of jaundice and capillary damage upon the various organs of the body. After a study of the pathology of this disease, Dawson, Hume, and Bedson²³ report that the principal changes are confined to the abdomen, especially the gastrointestinal tract, liver, kidney and biliary tract.

Any part or the entire gastrointestinal tract may be found peppered with petechial hemorrhages under the mucosal or serosal surfaces. Large hemorrhages into the wall of the intestines may occur and most commonly involve the duodenum. The duodenum shows a definite inflammatory reaction,²⁴ usually most marked about the ampulla of Vater. This affects that portion of the ductus choledochus within the duodenal wall, and it may become obstructed due to the edema and swelling, secondary to the inflammation.

The liver is usually slightly enlarged and bile stained,²⁵ but otherwise is grossly normal. It is never shrunk as in acute yellow atrophy. Microscopically, evidence of biliary stasis is found about the central portion of the lobules. Round cell infiltrations are scattered through the organ. The nuclei of the liver cells are swollen and often number two or three in a single cell. Bates²⁶ observed both focal and widespread necrosis of the liver parenchyma. Numerous other observations have been recorded but these are not significant.

The kidneys are usually slightly swollen, bile stained and frequently have subcapsular hemorrhages of varying size. In the majority of cases, the microscopic findings are confined to the tubules, though various degrees of focal and diffuse glomerulonephritis have been reported. The cells composing the tubules are swollen and necrotic. Various degrees of interstitial fibrosis and lymphocytic infiltration occur, and small capillary hemorrhages are quite characteristic.

The skeletal muscles, and more rarely cardiac muscle, show varying amounts and degrees of punctate hemorrhages, focal degeneration, loss of striations, and selective vacuolization of individual muscle fibers. Round cell infiltrations are commonly seen. A peculiar type of hyalinization¹⁵ of the muscle bundles, comparable though not resembling Zenker's hyaline degeneration as seen in typhoid fever, is considered quite characteristic of this disease.

The spleen is usually not enlarged. Heavy deposition of hemosiderin and numerous monocytes containing phagocytosed erythrocytes are the most common microscopic findings.

Two cases terminating in acute hemorrhagic pancreatitis²⁷ have been reported. Various pathologic changes in the skin, lungs, adrenals and other organs are described, but these simply reflect the effect of capillary damage and jaundice in the respective organ.

CLINICAL PICTURE.

Inada¹ defined three stages in the appearance of the clinical manifestations of this disease—A febrile or first stage, second, the icteric and hemorrhagic stage, and finally the convalescent or third stage. A description of the classical symptoms will be offered but the cases reported from the United States have rarely conformed to these definite divisions and have presented a much less acute picture.

TABLE I

	Symptoms and clinical findings											Demonstration of <i>Leptospira</i> by darkfield			Demonstration of stained <i>Leptospira</i> in sections or smears	Demonstration of <i>Leptospira</i> by guinea-pig inoculation				Final outcome
	Initial chill	Fever	Prostration	Jaundice	G. I. complaints	Nervous symptoms	Myalgia	Conjunctivitis	Hemorrhagic diathesis	Hepatomegaly	Splenomegaly	Leukocytosis	Blood	Urine		Bile	Blood	Urine	Cerebro-spinal fluid	
1	N	P	P	P	P	-	-	-	-	-	-	P	P	-	-	P	P	-	-	R
2	-	P	P	P	P	P	P	N	P	N	N	-	P	-	-	-	-	-	-	D
3	-	P	P	P	P	P	P	N	P	N	N	-	-	-	-	-	-	-	-	R
4	-	P	P	P	P	P	P	N	P	N	N	-	-	-	-	-	-	-	-	R
5	P	P	P	P	P	P	P	P	P	P	N	P	-	-	-	-	-	-	-	D
6	P	P	P	P	P	P	P	-	P	P	N	P	P	-	-	-	-	-	-	D
7	P	P	P	P	P	P	P	-	P	P	N	P	N	-	-	-	-	-	-	R
8	P	P	P	P	P	P	P	-	P	P	N	P	-	-	-	-	-	-	-	R
9	P	P	P	P	P	P	P	-	N	P	P	P	-	-	-	-	-	-	-	R
10	N	P	P	P	P	P	P	-	N	P	N	P	N	-	-	-	-	-	-	R
11	-	P	P	P	P	P	P	-	-	P	N	P	-	-	-	-	-	-	-	D
12	P	P	P	P	P	P	-	-	P	P	N	P	-	-	-	-	-	-	-	D
13	P	P	P	P	P	P	-	-	-	N	N	N	-	-	-	-	-	-	-	D
14	N	P	P	P	P	P	N	N	P	N	N	N	P	-	-	-	-	-	-	R
15	N	N	P	P	P	P	N	N	P	N	N	N	P	-	-	-	-	-	-	R
16	N	N	P	P	P	P	N	N	N	N	N	N	P	-	-	-	-	-	-	R
17	N	N	P	P	P	P	P	N	N	N	N	N	P	-	-	-	-	-	-	R
18	N	N	P	P	P	P	P	N	N	N	N	N	P	-	-	-	-	-	-	R
19	N	N	P	P	P	P	N	N	P	N	N	N	P	-	-	-	-	-	-	R
20	N	N	P	P	P	P	N	N	N	N	N	N	P	-	-	-	-	-	-	R
21	P	P	P	P	P	-	P	-	P	P	N	P	N	-	-	-	-	-	-	R
22	P	P	P	P	P	P	P	-	-	P	P	-	-	-	-	-	-	-	-	R
23	P	P	P	P	P	P	P	-	-	P	P	-	P	-	-	-	-	-	-	R
24	-	P	P	P	P	-	P	-	P	P	P	-	N	-	-	-	-	-	-	D
25	P	P	P	P	P	N	P	N	P	P	N	P	P	-	-	-	-	-	-	D
26	P	P	P	P	P	P	N	N	N	P	N	N	P	-	-	-	-	-	-	R
27	N	P	P	P	P	P	N	N	N	N	N	N	P	-	-	-	-	-	-	R

Code P = Present, palpable, or positive N = Not present, not palpable or negative
 - = Not mentioned or not performed R = Recovery D = Death

Febrile Stage After an incubation period of about one week the febrile stage is ushered in with the abrupt onset of chills, fever and severe prostration. These are followed by gastrointestinal disturbances and abdominal pain, nausea and epigastric colic being the most prominent of these symptoms. Headache and myalgia are frequent complaints. Occasionally, there is a cough, various cutaneous manifestations, and conjunctivitis, the latter being

considered a characteristic and important manifestation by numerous writers. This stage lasts seven to eight days, the above symptoms gradually becoming less severe as the second stage is approached.

TABLE II

		%
Positive Symptoms and Clinical Findings	Jaundice	100
	Prostration	100
	Fever	85
	G I Complaints	85
	Nervous Symptoms	74
	Hemorrhagic Diathesis	63
	Myalgia	63
	Hepatomegaly	59
	Initial Chill	48
	Splenomegaly	18
	Conjunctival Congestion	11
Positive Diagnostic Procedures	Darkfield Blood	52
	Stained Sections	33
	Guinea Pig Inoculation Urine	29
	Guinea Pig Inoculation Blood	25
	Darkfield Urine	7
	Guinea Pig Inoculation Mac Tissue	7
	Darkfield Bile	3
	Guinea Pig Inoculation C-S Fluid	3
	Mortality	40

Icteric or Toxic Stage Jaundice gradually appears in about 50 per cent of the cases, though it was reported in all of the American cases (see tables 1 and 2). A hemorrhagic diathesis occurs in a majority of cases, being more severe when icterus is present. It may manifest itself in the skin, conjunctiva, gums, or mucous membranes of the gastrointestinal and renal tracts. Marked weakness and nervous symptoms accompany the above manifestations. The liver becomes palpable and tender. Splenomegaly is absent in a majority of cases and is considered not characteristic of this disease. It is during this stage that death most frequently occurs if the case is destined to terminate unfavorably.

Convalescent Stage This stage begins about the third week and is characterized by the regression of all symptoms and the gradual diminution in the intensity of the jaundice. An after fever is seen in some cases and this may last from four days to three weeks. Inada² believes this fever is caused by the disintegrating toxins during the height of the serologic immunity.

Attention is again called to the fact that the American cases have been mild, 10 to 20 per cent remaining ambulatory throughout the course of the disease. A more practical description of the stages of this disease, based on laboratory findings, as related to clinical symptoms, has been proposed.¹⁵ This allows a more labile concept in the time of appearance, duration and severity of the symptoms. The first stage is characterized by the free circulation of *Leptospira*, by absence of humoral antibodies from the peripheral blood and by a lack of spirochetes in the urine. With the beginning of the

second stage, the number of *Leptospira* in the blood diminish and they begin to appear in the urine, while the antibodies increase in titer. During the third stage, the *Leptospira* in the urine are abundant at first after which they gradually diminish, but they cannot be found in the blood stream where well developed antibodies are now present. This conception of the disease explains many of the discrepancies in the appearance and duration of signs and symptoms reported in the American cases.

CLINICAL LABORATORY PROCEDURES

I Darkfield examination of blood, urine and bile

It is recommended that the blood and urine be examined according to the stage of the disease. Most authors claim that the *Leptospira* disappear from the blood on the ninth day, but this does not appear to be exactly true, since the organisms in the blood have been demonstrated as late as the sixty-first day.⁹ On the tenth day, they begin to appear in the urine persisting there as long as 60 days. The demonstration of spirochetes in urine seems to be much more difficult than in blood. We were able to find the organism in the bile. A method for obtaining adequate darkfield preparations was described earlier in this paper.

II Guinea pig inoculation

This is the usual and most satisfactory method of establishing the diagnosis of infectious jaundice. Five c c of whole blood, or spinal fluid, or 10 c c of freshly catheterized urine are injected intraperitoneally into guinea pigs. After an incubation period of five or six days the pigs become ill and heavily jaundiced. The animals die in from seven to ten days in most positive tests.

Guinea pigs may become ill but may fail to succumb to the disease; under these circumstances, they should be killed and examined on the tenth day.^{10b}

Postmortem examination reveals jaundice of the skin and other tissues, petechial hemorrhages into the skin and muscles of the abdomen, beneath the peritoneum and in the gastrointestinal mucosa, most characteristic are the hemorrhages over the surface of the lower lobes of the lung, which are spotted in appearance and suggest the wing of a mottled butterfly.²³ Acute congestion of and hemorrhages into the kidneys and adrenals are frequently encountered. *Leptospira* may be demonstrated in darkfield preparations of serum and liver emulsions. They may also be found in tissue sections of the liver and kidneys stained by Levaditi's method.

III Pfeiffer phenomena and immune guinea pig inoculation

This method consists of mixing the blood or urine to be injected with an equal amount of anti-serum. The mixture is then incubated at 37° C for one hour, after which it is injected intra-peritoneally as above. After one hour, repeated examination of the peritoneal fluid obtained by sterile capillary tubes will fail to show *Leptospira* while they may be demonstrated in the control animals which were inoculated without anti-serum.

The adequately protected pigs survive more than 12 days but may die later, from the fourteenth to the nineteenth day,²⁸ while the unprotected controls die in from the five to twelve days with the usual postmortem findings

IV. Blood culture

Culture of the patient's blood has been successful in the hands of some investigators. Manteufel²⁹ added 2 to 3 c c of blood to each of several sterile tubes containing 3 to 10 c c of sterile, distilled water. The tubes were then incubated three to four days at 25 to 30° C, and he found that at least one of the dilutions would show the organisms by darkfield examination. The *Leptospira* will live in this medium for three to four weeks.

V. Agglutination tests

These should be attempted after the tenth day of the disease. A titer of 1/100 is significant at this time. During the next four to six days, it rises rapidly to 1/1000, after which the titer may attain a maximum of 1/10,000 to 1/50,000 about the twenty-fifth day. In acute cases, failure of the titer to rise above 1/300 should cause suspicion as to the real identity of the disease in question. Following the convalescent period, the titer gradually decreases and by the end of the first year reaches a value of 1/300, where it remains rather constant for many years, if not throughout life. This test is of great value in diagnostic surveys of cases suspected of previous infection. It is not entirely reliable in the acute cases because of the persistent antibodies in previously recovered cases and because of the antigenic variation in the strains of *Leptospira*.

The complement fixation test has been used with marked success by Gaetgens³⁰ who found equally good positive results when compared with the agglutination tests. He claimed that the negative reactions were more clear cut with his method since the agglutination test with the lower dilutions is often questionable.

Recently, a precipitation test³¹ and an adhesion test³² have been described. Advocates of the latter test say that it is more rapidly performed and more easily read than the tests now in general use. As yet, none of the serological tests is available to all clinics, so most clinicians must rely on darkfield examination and guinea pig inoculations.

TREATMENT

A therapeutic serum is readily obtained by the immunization of horses or rabbits with cultures of *Leptospira icterohemorrhagica*. The serum is effective in man up to the fifth or sixth day of the disease, when injected intravenously in doses up to 60 c c in 24 hours. Most workers²¹ agree that the serum lessens the severity of the disease by reducing the duration of the jaundice and the extent of the hemorrhages. Others claim that the serum causes the blood to become free of spirochetes in a few days.

Reports as to the efficacy of convalescent serum vary, good results being obtained from sera which contain a high agglutinating and lytic titer.

Gaines and Johnson¹⁰ treated four patients with serum from recently recovered cases with good results. Either type of serum is indicated, if available, but is definitely of limited value.

Arsenicals have proved to be of no value in the therapy of Weil's disease.¹¹ They have been shown to be ineffective as Lepto-spirocheticidal agents, though neoarsphenamine will cause the organisms to disappear from the blood.²¹ The use of these drugs carries the added danger of further injury to an already damaged liver.

Bismuth Yatrien A, a soluble preparation of bismuth, has been used with success on experimental animals but, as yet, has not been used on man.¹

Symptomatic treatment is, of course, a necessity. A high carbohydrate, low fat, high vitamin diet is recommended. We found considerable symptomatic improvement in several cases following the daily injection of massive doses of liver extract.

PROPHYLAXIS

Prevention of the disease is most readily achieved by improvement of hygienic conditions in endemic districts, control of rats, disinfection or drainage of soil and water being of primary importance. Individual precautions include suitable protection against skin infection. Wani, Inada and Baerman, independently used methods of vaccination to establish active immunity in endemic districts and strikingly lowered the incidence in many instances. Active immunity on a large scale is not practicable but is recommended for use in certain groups constantly exposed to the infection.

DISCUSSION OF REPORTED CASES

In each of our cases the infection was definitely associated with rats. In case 2 we were able to demonstrate *Leptospira* in a living and dead rat from the immediate vicinity in which the disease had been contracted. So far as we have been able to determine, no other previously reported American case has been traced directly to the source. Case 1 was a W P A worker employed on a project in an old quarry, as were both cases reported by Mulholland and Bray^{11, 16}

In all the cases the disease had an acute onset which caused the patients to go to bed for several days, during which time the acute symptoms gradually subsided as the jaundice became manifest. Chills, fever or prostration heralded the onset of the disease in each case. These initial symptoms were found in the majority of the American cases (Tables 1 and 2). On admission, each of the patients was ambulatory and mentioned jaundice and pruritus as their chief complaints. The jaundice appeared from two to seven days after the onset and, during the course of the illness increased to a peak within two weeks, receded slightly, and then increased to a second peak somewhat higher than the first, gradually disappearing thereafter. In case 3 the

jaundice reappeared during the terminal phase of his illness. Though much has been written concerning *Leptospirosis* without jaundice, every case so far reported in the United States has had icterus.

From the patient's point of view in each of our cases, pruritus accompanying the jaundice was the most disturbing symptom. In case 3 the itching was so severe that the patient almost became psychotic. This symptom appeared to be the direct cause of the patient's nervous manifestations. In case 2 pruritus was the primary cause of the only hemorrhagic lesions seen in this patient. Other reports fail to mention this symptom or merely include it among the unimportant symptoms. Control of pruritus will control the nervous symptoms in a majority of cases.

A hemorrhagic diathesis appeared in case 1 nine months after the patient had acquired the infection and this seemed to be directly responsible for the patient's demise. These hemorrhages were traced to the gall-bladder mucosa, although the entire gastrointestinal tract was peppered with petechial hemorrhages.

Gastrointestinal complaints occur in 85 per cent of the reported cases. In case 3 these were limited to mild epigastric pain and nausea, but in case 1 these symptoms occurred during the first few weeks of the illness, disappeared for several weeks and reappeared as a typical, severe, biliary colic from the fifty-fifth to the sixtieth day, at which time it was believed that the patient had a complete obstruction of the bile duct. At operation, no stones or other lesions were demonstrated, but a cholecystogastrostomy was performed, after which his acute symptoms subsided. This has been observed in several other American cases in which the patients were operated on, one requiring a choledochoduodenostomy.⁹ Evidently, these patients had an intramural, inflammatory process upon the posterior wall of the duodenum, which could not be demonstrated by an anterior approach. Similar lesions have been described by Dawson and others.

Myalgia was a prominent complaint, occurring in 65 per cent of the other cases but was seen only in case 1 and this was very mild.

Case 3 presented a severe, persistent cough toward the end of the second stage at the height of the icterus. It was a most distressing symptom and prevented the patient from obtaining any rest. There was some speculation as to the exact cause of this symptom, some believing it to be due to *Leptospira* in the bronchi, while others attributed this manifestation to jaundice of the mucous membrane comparable to the pruritus which accompanies icterus of the skin.

Each patient noted, early in the disease, that his or her urine was dark and the stools clay colored. Bile pigments appeared in the stools in amounts indirectly proportional to the rise and fall of the icterus index values.

Enlargement of the liver occurred in both male patients, but was absent in the female. Case 1 exhibited the greatest enlargement which extended below the crest of the ilium and was associated with splenomegaly.

We were able to demonstrate *Leptospira* in the blood of each patient by darkfield examination and little difficulty was encountered. A method facilitating this procedure has been described. All the cases exhibited organisms in the blood after the ninth day, which is contrary to the findings of Inada and others. They were noted on the twenty-sixth, eleventh and nineteenth days of the respective illnesses. In the urine the *Leptospira* were more difficult to find and they were seen only in the second case on the twenty-second day of the disease. In case 1 the contents aspirated from the gall-bladder at operation contained *Leptospira* which were demonstrated by darkfield examination on the sixty-first day of the disease. Among the cases reported in the United States, this is the first case in which *Leptospira* have been demonstrated in the bile.

Though the possibility of human carriers has been doubted,¹⁷ we feel it is a real danger since *Leptospira icterohemorrhagica* have been demonstrated in human feces and urine by Frugoni and Cappellani,¹⁸ and many cases have been contracted in swimming pools which are well known to be contaminated from human sources. In case 1 the terminal pathology centered about the biliary tract which may have been a reservoir of infection.

Cases 2 and 3 were proved by guinea pig inoculations of the blood and urine on the fourteenth and twenty-fourth days, respectively. All four pigs died with typical necropsy findings, and *Leptospira* were demonstrated by darkfield in each animal.

In the American cases the organisms have been demonstrated in the blood by various methods after the ninth day of the disease, persisting as long as 63 days.⁹ From the present concept that *Leptospira* disappear from the blood as immune bodies appear, variation of the length of time that the organisms are found in the blood is to be expected, since it is well known that some individuals develop immunity more or less rapidly than others, and vary as to the maximum immunity attained. From these observations, the finding of *Leptospira* in the blood after the ninth day is not unusual. Most clinicians report difficulty in the demonstration of *Leptospira* in the urine by darkfield, although textbooks would lead one to believe that this is a simple procedure. Guinea pig inoculations of urine give much more satisfactory results.

In all cases the leukocyte count showed little variation which could be attributed to the disease per se, and this is substantiated in 50 per cent of the reported cases. The qualitative Van den Bergh test gave a direct, immediate reaction in case 1 while the reaction was biphasic in the other two. It would appear that this test merely reflected the amount of jaundice present in each case since it was direct during the periods of heavy jaundice. This is substantiated in other types of icterus.

It is interesting to note that the case in which a luetic infection could be least suspected had the only false positive Kahn reaction, as has been described by Manteufel.²⁰ This case is the third female to be reported in the

United States out of 27 reported cases. The marked difference in incidence is attributed to fewer occupational hazards.

In case 1 the necropsy findings were quite typical of the pathology described by others, including the finding of extensive liver necrosis as reported by Bates²⁰. The pathologic picture in this case reflects the duration and severity of the man's illness.

That this liver necrosis might have resulted in a primary hepatic failure in the formation of prothrombin was suggested by Dr. Albert M. Snell of Rochester, Minnesota. Under such circumstances, the hemorrhagic tendency might easily be explained upon prothrombin deficiency. Unfortunately, studies of this nature were not pursued, but it is suggested that all cases should be studied thoroughly from this angle.

Massive doses of liver extract were found to be of great value in the symptomatic therapy of this disease. The initiation of these injections was followed by a decrease in the icterus index values, which may, however, have been purely coincidental.

The general mortality from infectious jaundice thus far reported in the United States is 40 per cent, and our figure approximates this.

SUMMARY

Weil's disease is endemic in the United States and should be given consideration in the differential diagnosis of all icteric cases. In general, our cases resembled the cases previously described in this country. The acute onset of chills, fever and prostration which gradually diminish as jaundice and epigastric distress appear, should be a leading point in the consideration of this disease as a possible diagnosis. The majority of the American cases are indirectly associated with a history of rat contacts. We have traced one case directly to a colony of rats in New Jersey.

The application of a previously described method for obtaining adequate darkfield preparations has been suggested as a routine examination of all jaundiced patients. The persistence of *Leptospira icterohemorrhagica* in the blood after the ninth day of the disease has been definitely established in previous reports, as well as in our cases. The length of time that these organisms persist in the blood depends on the immunological response of each individual patient. We believe we have reported the finding of *Leptospira* in the bile for the first time in the American literature and suggest the possibility that the gall-bladder may act as a focus of infection and that the patient may become a human asymptomatic carrier of the disease. Demonstration of the *Leptospira* in the blood or urine by positive guinea pig inoculation is adequate proof of the disease. The agglutination test is not reliable but is of confirmatory value.

The possibility that prothrombin deficiency may play a rôle in some of the hemorrhagic manifestations of this disease has been suggested. To date, no studies have been reported on this subject.

Liver extract is of great value in the symptomatic therapy of this disease.

BIBLIOGRAPHY

- 1 WILK, H. A. : Über eine eigenthümliche mit Miltumoren, Icterus und Nephritis einhergehende, acute Infectiouskrankheit, Deutsch. Arch f klin Med, 1889, xxxv, 209-232
- 2 INADA, R, and IDO, Y : Tokyo Ishinshi, 1915, No. 1908, quoted by Inada et al."
- 3 INADA, R, IDO, Y, HOKI, R, KANIKO, R, and ITO, H. : The etiology, mode of infection and specific therapy of Weil's disease (spirochetosis icterohemorrhagica), Jr Exper Med, 1916, xxi, 377.
- 4 NOGUCHI, H. : Morphological characteristics and nomenclature of *Leptospira* (Spirocheta) icterohemorrhagica, Jr Exper Med, 1918, xxvii, 575
- 5 NOGUCHI, H. : Spirocheta icterohemorrhagica in American wild rats and its relation to the Japanese and European strains, Jr Exper Med, 1917, xxi, 755
- 6 MEYER, K. F., STEWART-ANDERSON, B., and EDDIE, B. : Leptospirosis, Am Jr Pub Health, 1939, xxix, 347
- 7 GAY, FREDERICK P., and Associates. : Agents of disease and host resistance, 1935, Charles C Thomas
- 8 WADSWORTH, A., LANGWORTHY, V., STEWARD, C., MOORE, A., and COLEMAN, M. : Infectious jaundice occurring in New York State, Jr Am Med Assoc, 1922, lxxviii, 1120
- 9 GAINES, A. R., and JOHNSON, R. P. : Weil's disease report of seven cases, Arch Int Med, 1937, lxv, 817-836
- 10 (a) McDOWELL, E. S. : A case of infectious jaundice, New York State Jr Med, 1925, lxxv, 19
 (b) CUSHING, E. H. : Leptospirosis icterohemorrhagica, Jr Am Med Assoc, 1927, lxxxix, 1014
- 11 MULHOLLAND, A. B., and BRAY, E. W. : Spirochetel jaundice, Jr Am Med Assoc, 1928, xc, 1113
- 12 TOWLER, H. H., and WAIKLE, J. E. : Spirochetel jaundice, Jr Am Med Assoc, 1927, lxxxix, 86
- 13 (a) SAILER, J. : Leptospirosis icterohemorrhagica (Weil's disease), Am Jr Med Sci, 1925, clxx, 332
 (b) HAYMAN, J. M., and LYNCH, F. B. : Leptospirosis icterohemorrhagica, Am Jr Med Sci, 1927, clxxiii, 8
- 14 BALL, A. H. : Leptospiral jaundice, Am Jr Clin Path, 1933, iii, 283
- 15 JEGHERS, H. J., HOUGHTON, T. D., and FOLEY, J. A. : Weil's disease, Arch Path, 1935, lxv, 447-476
- 16 MULHOLLAND, H. B., and BRAY, W. E. : Weil's disease, report of a case with autopsy findings, Internat Clin, 1937, iv, 122-126
- 17 LITTLE, O. W. : Spirochetosis icterohemorrhagica, report of three cases, Texas State Jr Med, 1936, xxxii, 305-306
- 18 MOLNER, J. G., and KASPAR, J. A. : Outbreak of jaundice in Detroit, preliminary report, Jr Am Med Assoc, 1938, cx, 2069-2070
- 19 KEENEY, PAUL A. : Personal communication, Asst Director Bureau of Health Conservation, State of Pennsylvania, April 26, 1939
- 20 FRIEDMAN, L., and MAZER, M. L. : Detection of syphilis in urological clinic, Am Jr Syph, Gonorr and Ven Dis, 1938, xxii, 340-345
- 21 INADA, R., IDO, Y., HOKI, R., ITO, H., and WANI, H. : Intravenous serotherapy of Weil's disease, Jr Exper Med, 1918, xxvii, 283
- 22 COSTA, S., and TROISIER, J. : Infections experimentales subaigues et chronique par inoculation de *B. icterogenes*, Compt rend Soc d biol, 1916, lxxix, 703
- 23 DAWSON, B., HUME, W., and BEDSON, S. : Infective jaundice, Brit Med Jr, 1917, ii, 345
- 24 STOKES, A., RYLE, J. A., and TYTLER, W. H. : Weil's disease in the British Army in Flanders, Lancet, 1917, i, 142

- 25 GARNIER, M, and RIVIÈRE, J Étude anatomique du foie dans la spirochetose ictérigène chez l'homme, Arch de med exper et d'anat path, 1919, *xxviii*, 228
- 26 BATES, J H Leptospirosis icterohemorrhagica (Weil's disease), Canad Med Assoc Jr, 1926, *xi*, 1466
- 27 MAYER, A Veränderungen der Bauchspeicheldrüse bei der Weilschen Krankheit, Deutsch med Wchnschr, 1918, *xiv*, 857-860
- 28 IDO, Y, HOKI, R, ITO, H, and WANI, H The rat as a carrier of *Spirocheta icterohemorrhagica*, the causative agent of Weil's disease, Jr Exper Med, 1917, *xxvi*, 341
- 29 MANTEUFFEL, P Vereinfachung des Zuchtungsverfahrens von Weil Spirochäten, Deutsch med Wchnschr, 1921, *xvii*, 461
- 30 GAERTGENS, W Beitrag zur Serodiagnose der Weilschen Krankheit, Klin Wchnschr, 1933, *xii*, 697-698
- 31 HINDLE, E, and WHITE, P B Soluble specific substances in spirochetes, Proc Roy Soc London, 1934, *cxiv*, 523-529
- 32 BROWN, H C Serological diagnosis of Weil's disease, Brit Med Jr, 1935, *i*, 411
- 33 FRUGONI, C, and CAPPELLANI, S Intorno all' eziologia dell' ittero epidemico, Riforma med, Napoli, 1917, *xxxiii*, 439, quoted by Jeghers, et al ¹⁵
- 34 SNELL, ALBERT M Personal communication, Mayo Clinic, Rochester, Minnesota, November, 1939

THERAPEUTIC STUDIES IN HYPERTHYROIDISM *

By PAUL STARR, M D , and HERMAN POMERENZI, M D., *Chicago, Illinois*

For several years attempts to suppress hyperthyroidism by various medicaments have been carried out in our clinic. The rationale of this project is furnished by the occurrence of spontaneous remissions occasionally observed in this disease and the physiological demonstration of a chalone type of mechanism in other endocrine relationships. Of the latter, pituitary suppression by estrogens, inhibition of lactation by androgens, and estrogen neutralization by progestin, may be mentioned. It would seem probable, therefore, that a physiological control of the over-active thyroid would be possible if a condition or substance acting as a chalone for the thyroid could be discovered.

I *Spontaneous Remission of Acute Puerperal Hyperthyroidism*

Case 1 Mrs. A. L., aged 27 years, white, married. Her third pregnancy terminated normally on August 29, 1935; she nursed her baby. She was fatigued and intolerant to physical exertion, but did not have distinct complaints until after an acute sore throat on November 25, i.e., three months postpartum. After this the usual symptoms of severe thyrotoxicosis were pronounced. Amenorrhea associated with lactation was present. The basal metabolic rate on December 26, 1935 was +56 per cent, pulse 136, weight 115 pounds, on January 8, 1936, the metabolic rate was +54 per cent, pulse 100, weight 115 pounds. She was ordered to wean her baby on January 4, 1936. No iodine was given. The rapid subsequent fall of metabolic rate is indicated in figure 1. Menstruation occurred 31 days after cessation of nursing, i.e., on February 4, 1936. On February 14, after 41 days, the metabolic rate was +6 per cent, the pulse 68, weight 118 pounds. Menstruation occurred regularly at 31 day intervals. In May of 1936 a test of responsiveness to thyrotropic hormone was carried out as indicated. No significant reaction occurred.

Interpretation It seems possible that a thyroid inhibitory mechanism was developed during the readjustment from lactation to menstruation, that is, with the return of cyclic production of follicle stimulating pituitary hormone. That this condition had a chalone effect upon the thyroid is evidenced by the failure of the thyroid to respond to effective doses of thyrotropic hormone (see Starr 1937 and 1940). This suggests that the subsidence of hyperthyroidism was due not merely to the withdrawal of thyroid stimulation, a mechanism entirely possible, but to active inhibition by a chalone mechanism that persisted in force for some months.

II *Remission Associated with Gonadotropic Treatment in Puberty*

Case 2 Miss G. DeF., a single Italian immigrant girl, 17 years of age, had lived in Chicago since the age of 7 years. At the age of 10 thyroid enlargement was noted. Her family physician administered Lugol's solution for three months when she was

* Received for publication August 5, 1940.

From the Department of Medicine, Northwestern University Medical School, Chicago

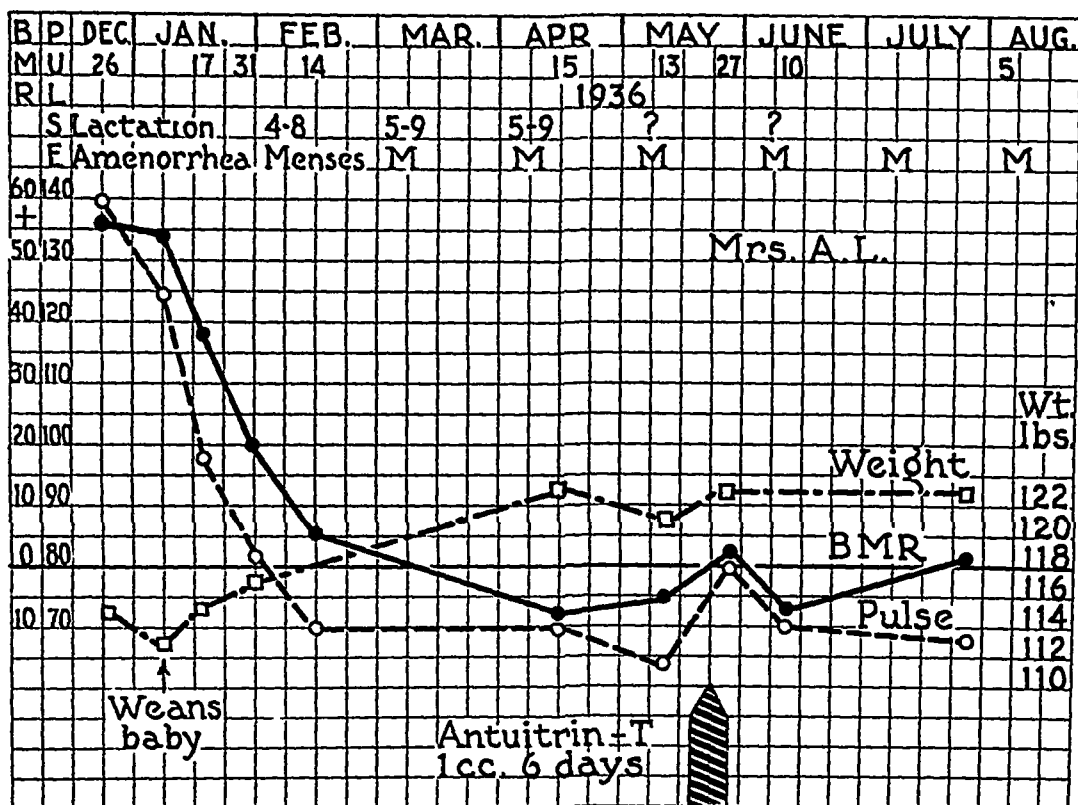


FIG 1 (Case 1) Mrs A L Example of remission of hyperthyroidism coincident with cessation of lactation and return of menstruation

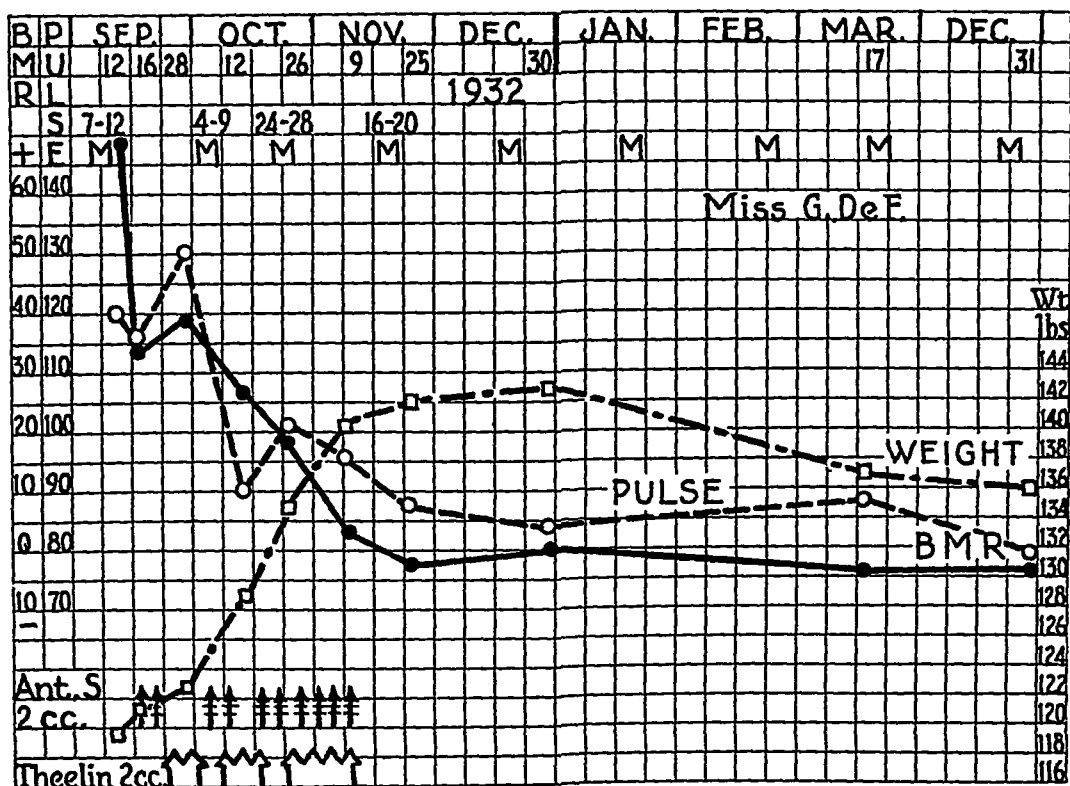


FIG 2 (Case 2) Miss G DeF Example of remission of hyperthyroidism coincident with treatment with chorionic gonadotropin and theelin

16 years of age. When admitted to the clinic in September 1932 she had had no iodine for six months. The thyroid was symmetrically enlarged to a slight degree. No exophthalmic signs were present, the pulse rate was 144. Other neuromuscular evidences of hyperthyroidism were present. Menstruation had been and continued regular. The first basal metabolic rate was -1 67 per cent, pulse 132, weight 119 pounds. A control rate four days later, however, was -1 31 per cent, pulse 120, weight 121 pounds. Antutrin-S was given after menses and theelin before menses. The dramatic subsidence of hyperthyroidism is indicated in figure 2. When examined in December 1933, 15 months after admission, the patient's basal metabolic rate was -4 per cent, the pulse 76, weight 136 pounds. She had no evidence of hyperthyroidism and had been doing factory labor for eight months.

Interpretation. It seems possible that the gonadotropic action of the anterior-pituitary-like hormone and the intermittent use of theelin induced an endocrine thyroid chalane mechanism. The pubertal state may be particularly favorable to this reaction. Subsequent experience was reported (Starr and Patton).

CLINICAL STUDIES

III *Desiccated Thyroid Combined with Lugol's Solution*

The therapeutic administration of thyroid to patients with hyperthyroidism who already have an excess of thyroid hormone in their tissues is, nevertheless, plausible because of animal demonstration that substitution therapy inhibits the gland of origin (thyroid atrophy) and suppresses the pituitary production of tropic hormone for that gland (Kundy, 1928, Kuschinsky, 1933).

Case 3. Mrs. A. S. was observed in 1930, 1931 and 1932 (figure 3). Five control metabolic rates from August 1930 to February 1, 1931 averaged $+40$ per cent. On Lugol's solution, without thyroid, the rate dropped to $+28$ per cent. Lugol's solution was continued throughout the remaining months of observation. Desiccated thyroid, 4 grains daily, was begun on February 7. After one month of this combined medication the metabolism was only $+32$ per cent. This suggests that the endogenous hormone was being reduced by the iodine solution as the exogenous thyroid was accumulating. Later, in April and May, the rate rose to $+58$ per cent, as it may be supposed that the patient's thyroid was "escaping" from the Lugol's control. At the time of this increase the daily thyroid dosage was decreased to 2 grains and maintained at this level for three months, during which time the basal metabolism declined gradually to $+35$ per cent, a further reduction in dosage to 1 grain daily was followed by a gradual decline to $+20$ per cent in November 1931. Both medications were continued until the middle of May 1932. Three weeks after the discontinuance of the thyroid medication the metabolism was $+26$ per cent.

Case 4. Mrs. J. D., aged 32 years, typical hyperthyroidism with exophthalmos and amenorrhea. She was observed on Lugol's and desiccated thyroid for a year before successful thyroidectomy. The control metabolism tests in March 1931 were $+34$ per cent on the seventeenth and $+34$ per cent on the twentieth. Large doses of desiccated thyroid—6, 8 and 4 grains a day—combined with Lugol's solution, were followed by an immediate drop, with a succeeding high plateau and, later, a depression which was finally succeeded by a recurrence when smaller doses of thyroid were used. The general course is similar to that in case 3.

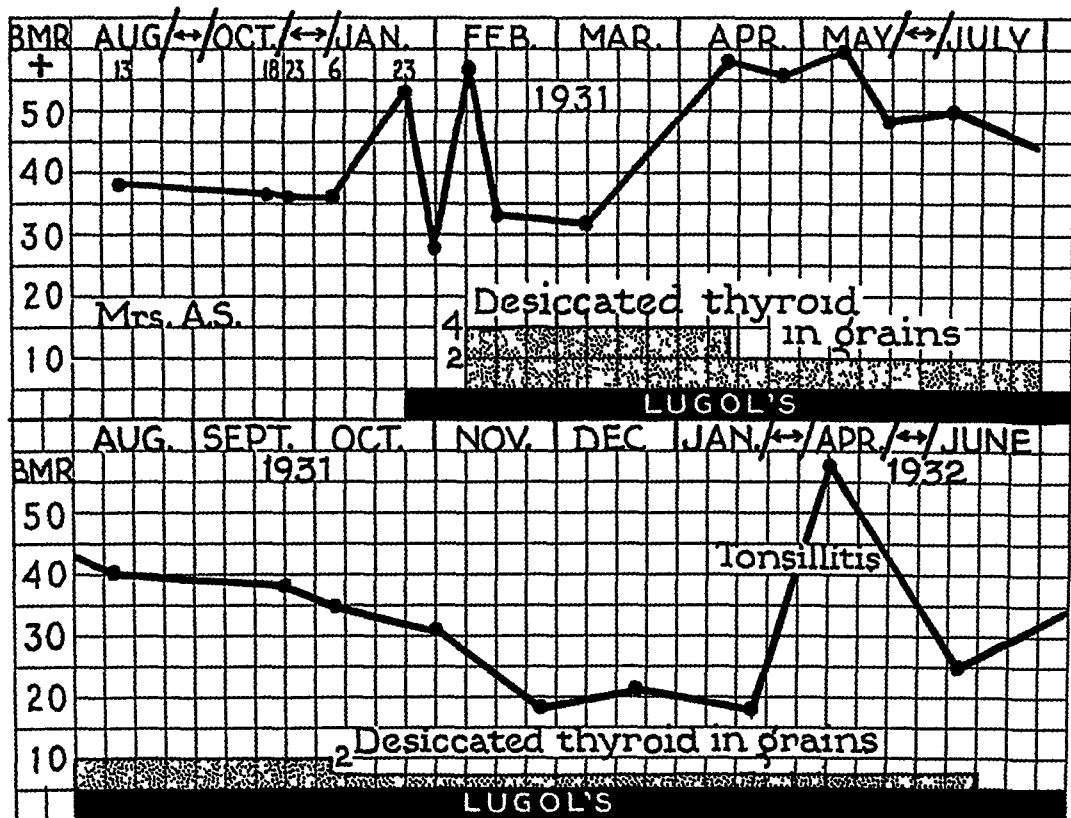


FIG 3 (Case 3) Mrs A S Example of effect of prolonged iodine and oral thyroid medication in hyperthyroidism

Case 5 Mrs A P, aged 58 years, had had a goiter for five years, which had become toxic, with definite symptoms of hyperthyroidism during the past two years. She was observed from November 9, 1931 until February 19, 1932. Three control metabolic rates were +41, +25 and +34 per cent. No iodine was administered. She was put on desiccated thyroid, 1 grain daily, on November 30, and this was increased to 3 grains a day on December 14. The basal metabolic rate dropped to +26.5 per cent on December 28, the thyroid dosage was then increased to 5 grains a day and continued until February 19, 1932. The metabolic rate gradually dropped to +22.5 per cent and her clinical symptoms improved considerably. She then left the city and was not seen again.

Case 6 Mrs M C, aged 26 years, showed mild hyperthyroid symptoms with slight suggestion of exophthalmos. A control metabolic rate was +30 per cent. On June 19, 1931 she was placed on 6 grains of thyroid daily for three weeks, the basal metabolic rate rose to +48 per cent and she lost eight pounds in weight, although her nervousness and emotionalism decreased somewhat. On July 10 the thyroid dosage was reduced to 4 grains a day, the metabolic rate continued to rise, and on July 24 it was +50.4 per cent, although she stated that she felt better. The thyroid dose was again reduced—to 2 grains a day—and continued until October 5, during this time the metabolic rate gradually dropped to +6.5 per cent on October 5 and her symptoms improved markedly. The thyroid medication was then stopped and she was put on 1½ grains of phenobarbital daily. Throughout the month of October she continued to feel fairly well but during the first week of November she had an attack of influenza which kept her in bed for 10 days. Following this she became restless and could not sleep. On November 23, 1931 the basal metabolic rate was still only +6 per cent, but

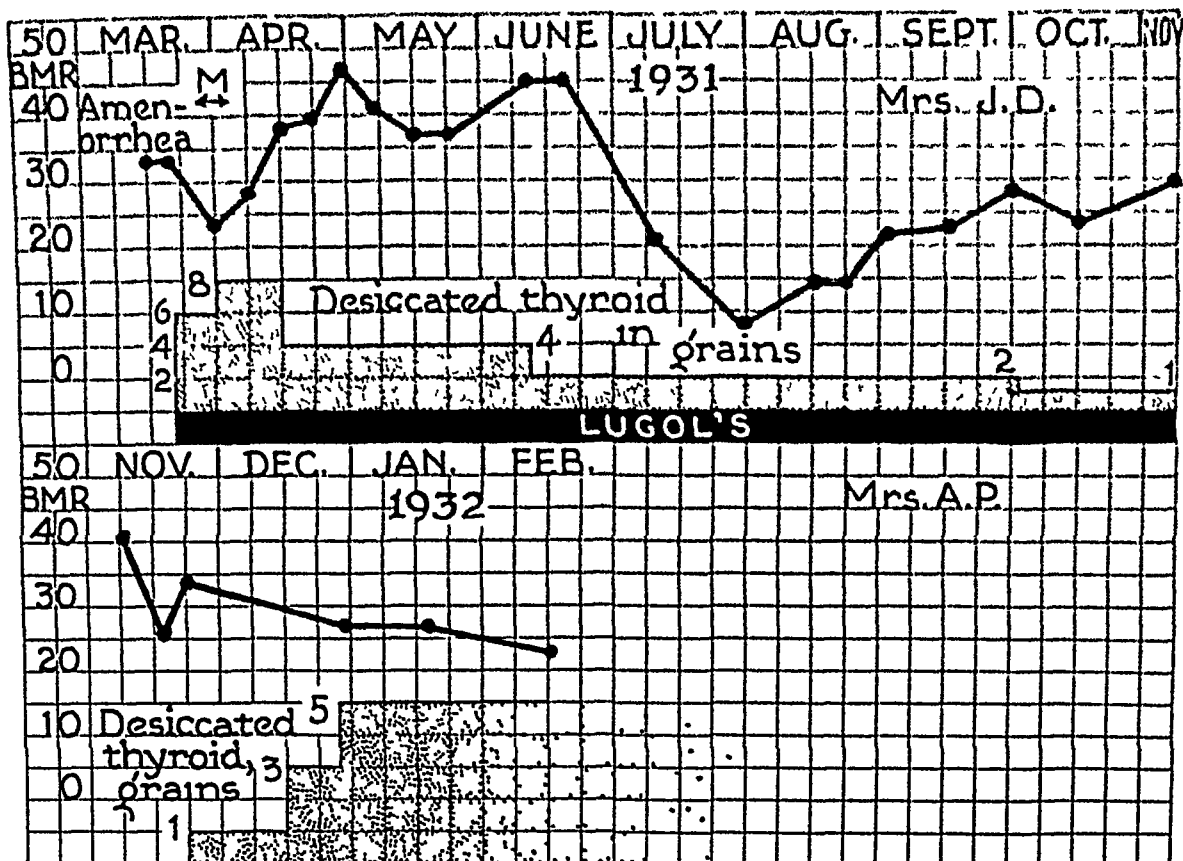


FIG 4 (Case 4) Mrs J D Example of effect of prolonged iodine and oral thyroid medication in hyperthyroidism

FIG 5 (Case 5) Mrs A P Example of absence of additive calorigenic action of oral desiccated thyroid in hyperthyroidism

she complained of diarrhea, sleeplessness, nervousness and, especially, marked exophthalmos. In fact, the exophthalmos was the dominating and most interesting feature in this case. When the patient was first seen there was only a suggestion of exophthalmos, although basal metabolic rates of +30 and +48 per cent were found, but, in spite of a gradual decrease in the metabolic rate and marked general improvement, the exophthalmos became progressively worse and a thyroidectomy was advised and performed in November, in spite of the normal basal metabolic rate and rather mild subjective symptoms, mainly because of the progressive exophthalmos.

Case 7 Mrs. K. T., aged 35 years, was under observation in our clinic from August 1931 until January 1935. When first seen she presented typical symptoms of hyperthyroidism, with definite eye symptoms, the basal metabolic rate was +44 per cent. On August 10, 1931 she was put on Lugol's solution, 20 drops, and thyroid, 6 grains daily, and placed on a high caloric diet. This treatment was continued until September 18, 1931, when the thyroid was reduced to 3 grains and Lugol's to 10 drops daily, there had been little change in the metabolic rate since the beginning of treatment but the subjective symptoms had improved considerably. When seen on September 24 she complained of having suffered from severe headaches for a week, and the thyroid was again increased to 6 grains a day. On October 2 the basal metabolic rate was +57 per cent, but the headaches had disappeared. This treatment was continued until October 9, when the thyroid was reduced to 3 grains and the Lugol's reduced to 15 drops daily, and whole pituitary, 3 grains a day, was added. She felt much better, although the metabolic rate rose slowly to +49 per cent on October 16 and to +58 per cent on December 21. The pituitary was discontinued on December

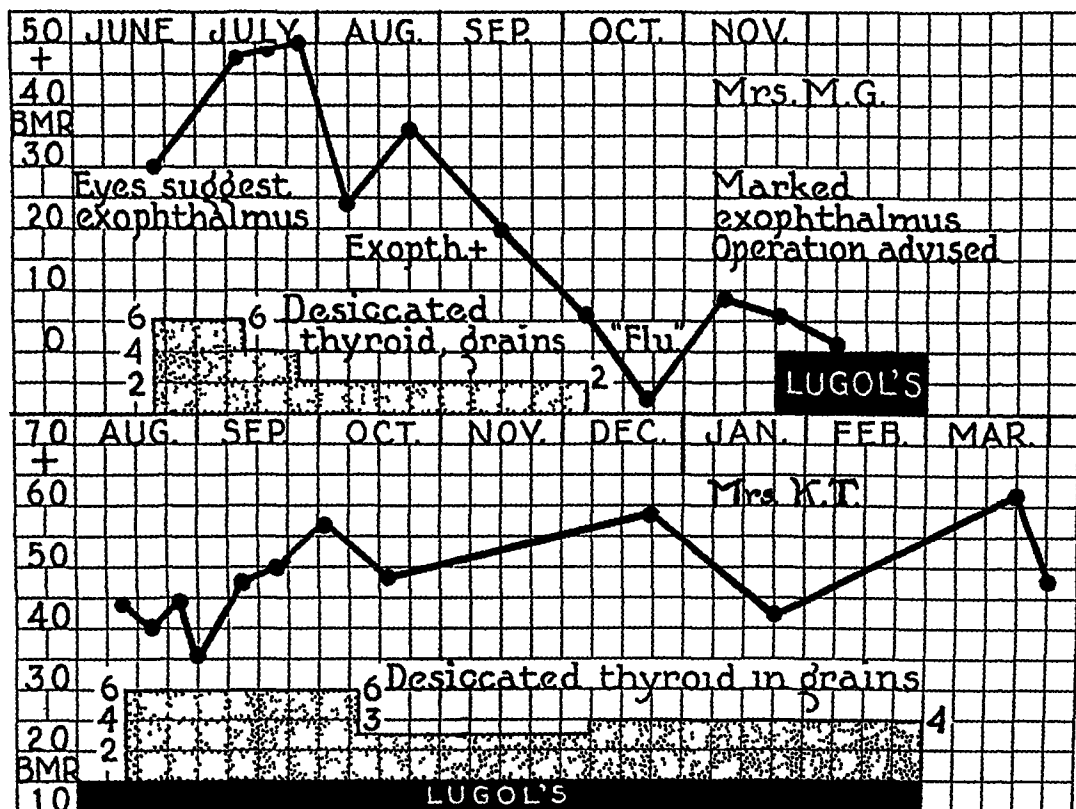


FIG 6 (Case 6) Mrs M G Example of falling basal metabolic rate and progressive exophthalmos with oral desiccated thyroid in hyperthyroidism

FIG 7 (Case 7) Mrs K. T Example of effect of prolonged iodine and oral desiccated thyroid in hyperthyroidism

7, and the thyroid was again reduced to 4 grains daily. She gained weight and continued to work hard in spite of the increasing metabolic rate. On December 28 the thyroid dosage was reduced to 2 grains a day and continued at that amount until March 1, 1932, when all medication was stopped. The metabolic rate rose to +64 per cent on March 21, and her subjective symptoms became aggravated. She was then put on Lugol's, 15 drops daily, and on a 2 per cent sodium fluoride solution, 30 drops daily. These were continued until April 11, at which time the thyroid gland seemed to be reduced in size but firmer in consistency, with a bruit over both lobes. The Lugol's solution was then increased to 20 drops daily. The patient did not return to the clinic until January 15, 1935, after an interval of nearly three years. She stated that during the year 1933 she gained weight up to 138 pounds (her weight on March 28, 1932 was only 108½) and felt very well and perfectly normal until May 1934. Her home surroundings were also much better during that period. In May 1934 she had an attack of some stomach or gall-bladder disease lasting about three weeks, during which time she lost 16 pounds. She said that she had been taking Lugol's, 20 drops daily, from September 1934 until three weeks before she returned to the clinic, and that she had not felt any different since stopping the Lugol's. Examination on January 15, 1935 showed no evidence of toxicity, her weight was 134¼ pounds, the pulse 92. There was no tremor. The thyroid gland was smooth, enlarged, firm and symmetrical, the skin warm, she was then in the seventh month of pregnancy.

Comment Cases 3, 4 and 7 indicate the persistence of hyperthyroidism when large doses of iodine and desiccated thyroid are combined. Variations

in the metabolism over long periods of time present modifications of the usual course of hyperthyroidism under iodine (Starr 1927). Cases 5 and 6, hyperthyroidism treated with desiccated thyroid without iodine, are extraordinary. In case 6 the metabolic rate was raised from ± 30 to ± 50 per cent by massive initial thyroid medication and withdrawal was followed by remission, but this effect was accompanied by an increase of exophthalmos which, of itself, warranted thyroidectomy. Case 5 was not followed to conclusion. The control rates of ± 40 , ± 25 and ± 34 per cent are satisfactory. Gradual increase of thyroid medication was not followed by increased basal metabolic rate.

IV *Effect of Thyrotropic Hormone in Hyperthyroidism*

All pituitary extracts containing the various pituitary tropic hormones tend to develop a specific immunity when used in animals for a prolonged period of time. Whether this immunity is brought about by the presence of specific antihormones in these extracts, as suggested by Collip, or by specific antibodies developed by the protein impurities of the extracts, is still a disputed point. That such an immunity does develop has been well established by numerous investigators and may be said to have been generally accepted. However, the role of the thyrotropic hormone, both in the development and in the course of human hyperthyroidism, has not been definitely established. In the cases presented here we have attempted to influence the course of human hyperthyroidism by injecting varying doses of thyrotropic hormone with the object of developing an immune state antagonistic to the disease.

Case 8 Mrs J. A., 55 years of age, came to the clinic with an indefinite story concerning her thyroid disturbance. She stated that she was not nervous, had no heart consciousness and no excessive perspiration, but had noticed a small goiter, she had lost some weight as a result of dieting. The effect of Lugol's on the basal metabolic rate was rather questionable, as indicated in figure 8. From March 11 to April 23 she received no specific medication except cod-liver oil and phenobarbital, both of which were discontinued on the latter date. On May 29, 1935 she was given antuitrin-T,* $\frac{1}{2}$ c c for four days, unfortunately, the immediate effect was not measured. The basal metabolic rate on June 18 was ± 38.5 per cent, although she stated that she felt better than before the injections. One-half c c of antuitrin-T was given daily from July 10 to 16, on July 17 the metabolic rate was ± 58 per cent, but the patient had no complaints, she was given elixir of phenobarbital which she continued to take until August 13. At that time she felt very well and all medication was stopped. The basal metabolic rate on October 11, 1935 was ± 26 per cent, the pulse 72, she had no complaints whatsoever. She returned to the clinic on July 15, 1937, when her basal metabolic rate was ± 27 per cent, without subjective symptoms. A third test of responsiveness to thyrotropic hormone was made. Basal metabolic rates on July 15 and 29 were ± 27 and ± 20 per cent respectively. Six injections of 1 c c each were given from August 11 to 18, 1937, the metabolic rate on August 19 was ± 29 per cent, indicating non-significant variations in tests.

* Generously furnished by Dr E. A. Sharp, Parke Davis & Company

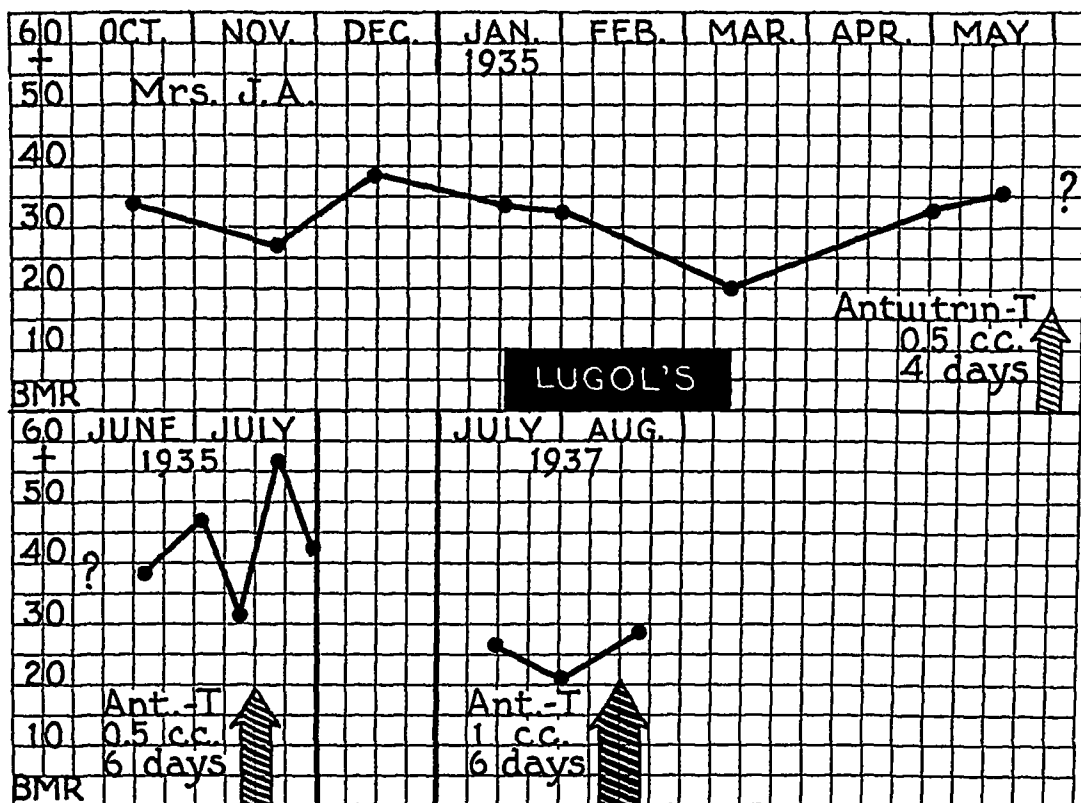
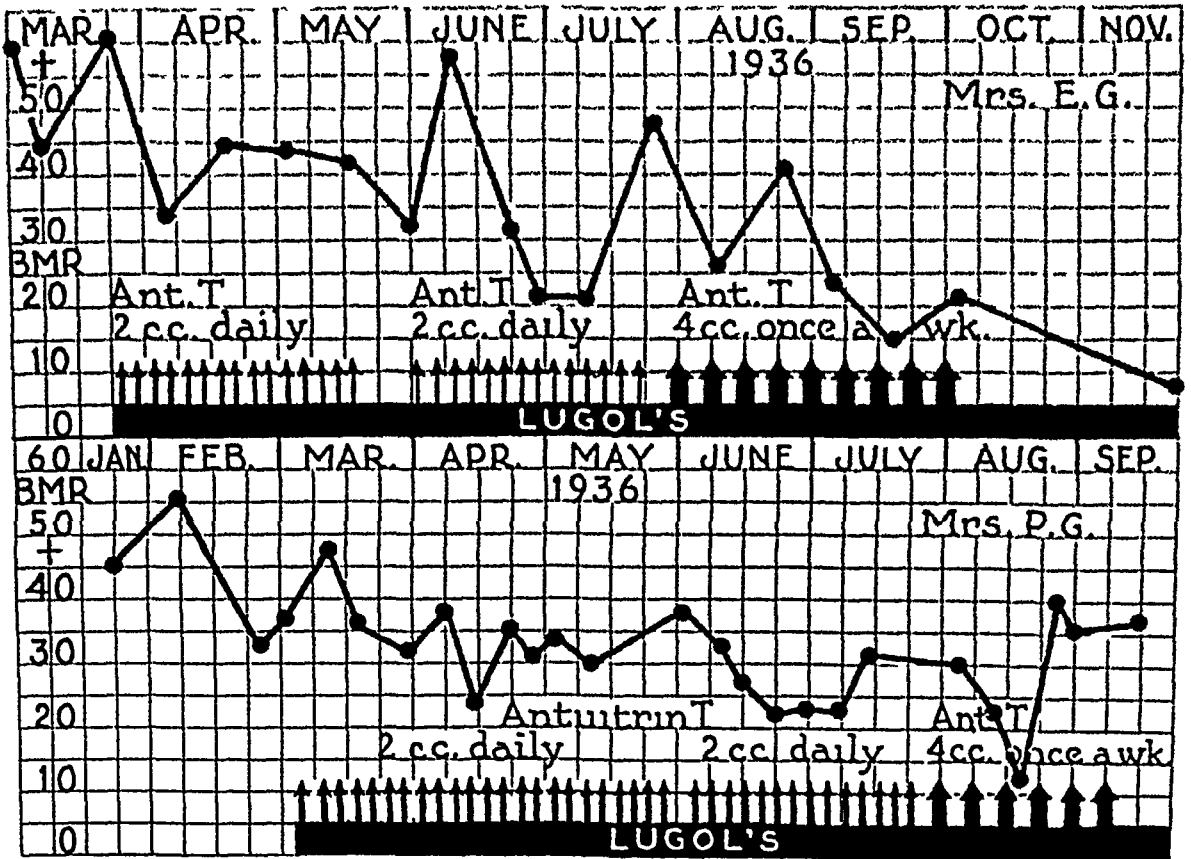


FIG 8 (Case 8) Marked response to thyrotropic injections in 1935, absence of response to double the dose in 1937, suggesting development of chalane

Comment Response to thyrotropic injections in July 1935, from an average control rate of + 40 to + 57 per cent indicates lack of chalane as compared to the non-significant reaction in August 1937, when the clinical course was approaching recovery

Case 9 Mrs E G, aged 37 years, presented herself at the clinic on February 2, 1936, with a large pulsating thyroid and subjective and objective symptoms of hyperthyroidism. The control basal metabolic rates were + 59.2 per cent on February 29, + 44 per cent on March 10, and + 62 per cent on March 21. On March 24 she was placed on Lugol's solution, 15 drops three times a day, phenobarbital, 3 grains a day, and antutrin-T, 2 c c daily. This treatment was continued until May 16, 1936 (when the patient left the city for a vacation) with exception of the phenobarbital which was discontinued on April 7. During this period the basal metabolic rate fluctuated between + 34 and + 45 per cent and her subjective symptoms improved considerably.

On June 1 she returned, stating that she was feeling fine and had gained about 20 pounds in weight. The basal metabolic rate on that date was + 32 per cent, the pulse 96. She was again put on antutrin-T, 2 c c daily. The metabolic rate on June 9 was + 58 per cent and on June 20, + 32 per cent. On the twentieth she returned to work, feeling very well. The antutrin-T was continued daily until July 22, after which 4 c c were given once a week, the weekly injections were continued until October 3, and when last seen on February 7, 1939, she was still taking the Lugol's solution. There was a definite remission, both subjectively and objectively, the basal metabolic rate fluctuated, but at a much lower level, i e, between + 10 and + 15 per



FIGS 9 and 10 Examples of effect of prolonged treatment with thyrotropic hormone and iodine in hyperthyroidism. Note figure 11, that marked response to thyrotropic injections occurred in November 1934, August 1935 and September 1935, suggesting absence of chalone.

cent. She stated that she held a job which required much activity, walking and stair-climbing.

Case 10 Mrs. P. G., aged 44 years, presented a definite hyperthyroidism with slight exophthalmos. Two control basal metabolic rates were +45 per cent on January 24, 1936, and +56 per cent on February 4. She was placed on a high caloric diet, milk, and tincture of belladonna, this was continued until March 2 when the metabolic rate was +36 per cent and the pulse 90. She was then put on antutrin-T, 2 cc daily, and Lugol's solution, 5 drops three times a day. On this treatment the metabolic rate first rose to +48.5 per cent, then gradually declined to +36.5, +31.5, and finally to +23 per cent on April 13. After five weeks of treatment she seemed less toxic, the tremor disappeared, she ate and slept well, and the thyroid gland seemed smaller and harder. The antutrin-T injections were stopped on May 27, started again on June 2 and continued throughout June, July and August. Although her subjective symptoms practically disappeared, the basal metabolic rate fluctuated between +11 and +40 per cent, and the pulse between 80 and 100. On September 8 the antutrin-T injections were discontinued and thyroidectomy was advised, the basal metabolic rate at that time was +35 per cent. On September 15 she reported that she did not feel as well as she had while taking the antutrin-T. A thyroidectomy was performed on October 22.

Case 11 Miss D. H., aged 34 years, gave a history of thyroid disease at irregular intervals since 12 years of age. The degree of hyperthyroidism on admission to the clinic in May of 1934 was mild. Observation and treatment with various amounts of theelin and antutrin-S did not lead to remission. The general average of

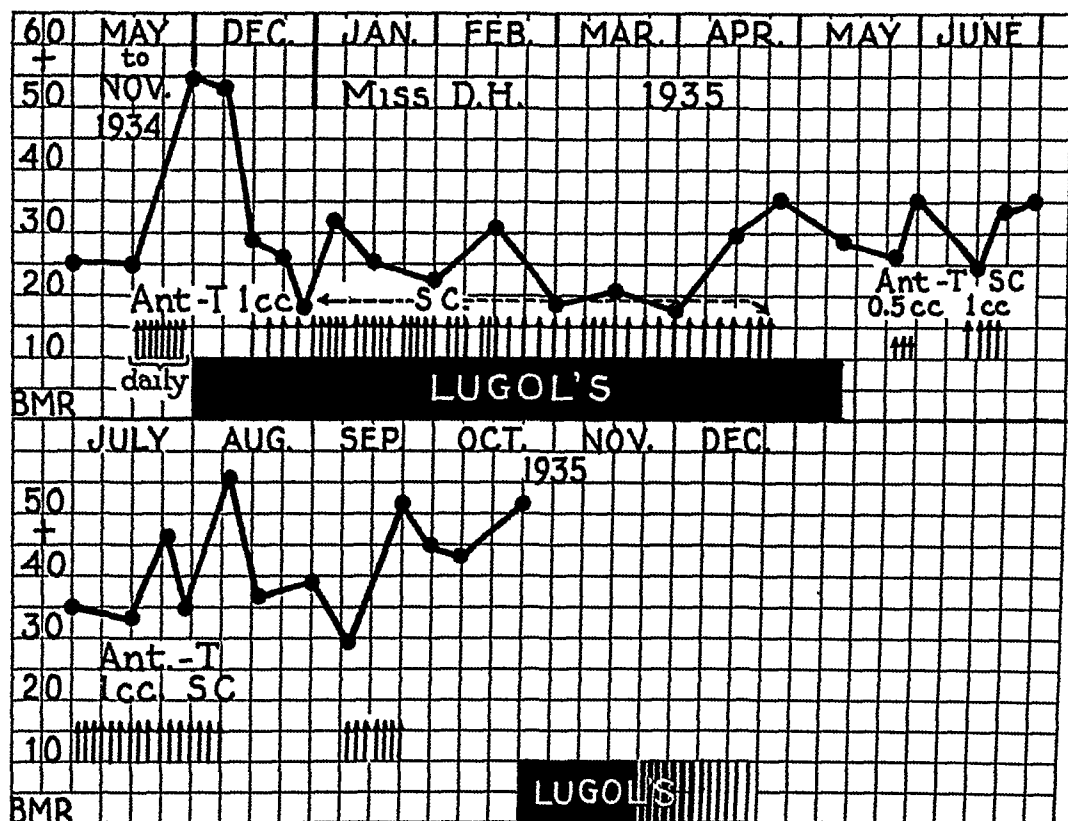


FIG 11 Examples of effect of prolonged treatment with thyrotropic hormone and iodine in hyperthyroidism. Note figure 11, that marked response to thyrotropic injections occurred in November 1934, August 1935 and September 1935, suggesting absence of chalone

basal metabolic rate determinations from May to November was $+25$ per cent. Antutrin-T, 1 cc daily for eight days, produced a sudden aggravation of symptoms and a rise of metabolism to $+55$ per cent. Lugol's solution was immediately started and continued for five months. When the rate had returned to $+29$ per cent antutrin-T, 1 cc every other day, was given for four months. No inhibitory effect was produced. Lugol's solution was discontinued. Two months' treatment with antutrin-T alone did not produce a sustained elevation of metabolism, but after a two week interval seven injections produced a rise of metabolic rate from $+30$ to $+52$ per cent.

This case demonstrates the exaggerated responsiveness of the hyperthyroid patient to thyrotropic hormone and that Lugol's solution will protect the patient's thyroid from the thyrotropic hormone. Moreover, prolonged treatment intermittently from December to September with thyrotropic hormone did not create antihormone which would affect the disease process or diminish the response to injections.

Case 12 Mrs W R, aged 29 years, presented herself on October 1, 1935, with a fairly well established hyperthyroidism, with slight exophthalmos. She gave a history of previous attacks of thyrotoxicosis followed by remissions. Three control basal metabolic rates of $+30$, $+41$ and $+30$ per cent were obtained. On November 12, 1935 she was placed on Lugol's solution, 10 drops twice a day, this was continued throughout the entire course of treatment. Two weeks after starting the

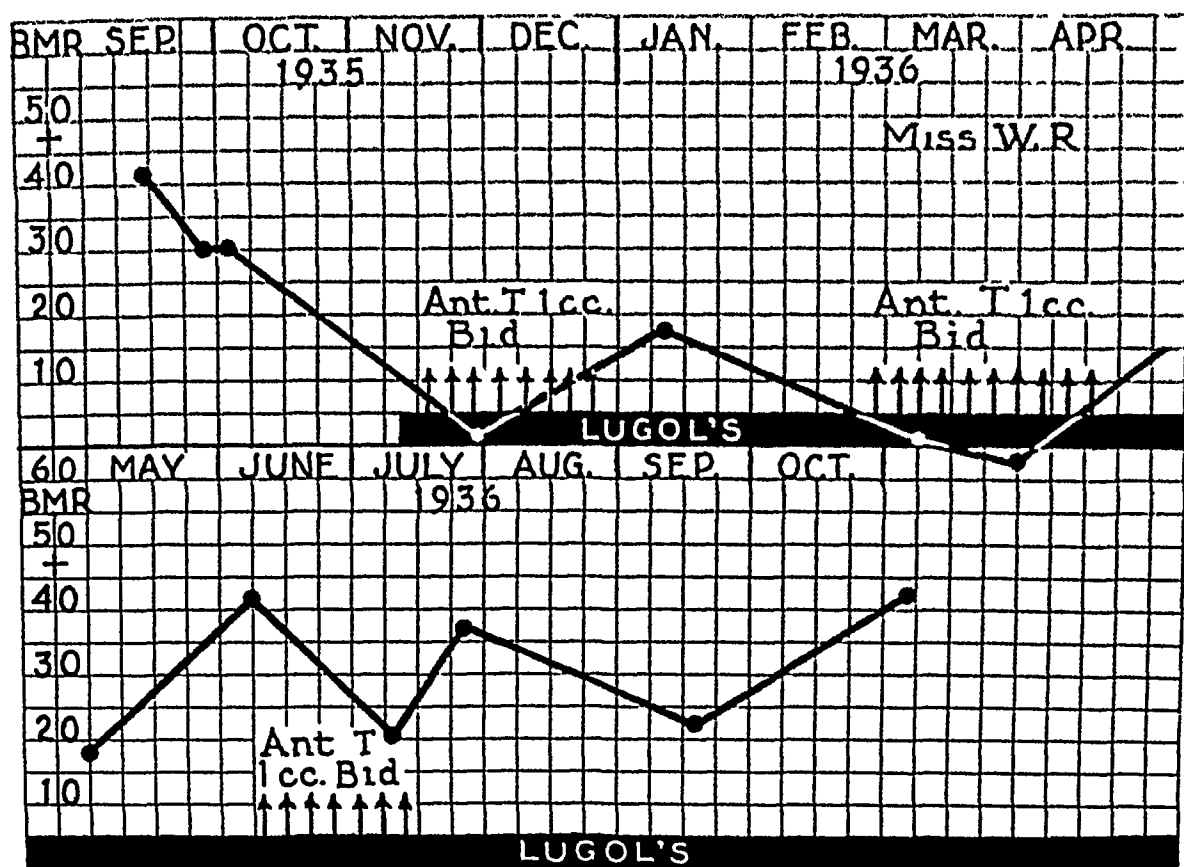


FIG 12 (Case 12) Miss W R Example of subsidence and recurrence of hyperthyroidism during iodine treatment

Lugol's there was a definite iodine remission, and the basal metabolic rate on November 26 was -0.5 per cent. On the same day antuitrin-T, 1 cc twice daily, was added to the treatment and continued until December 24, it was again given from February 27 to April 14, 1936, and from June 10 to July 25. The basal metabolic rate fluctuated very markedly, as indicated in figure 12. On July 25, 1936 she stated that she felt very well but was tremulous when nervous. The pulse was 100, the thyroid firm and nodular. The general impression was that the thyrotoxicosis was under good control but not eliminated. Antuitrin-S, 1 cc daily for seven days, was then given in place of the antuitrin-T. On September 17, 1936 the basal metabolic rate was $+21$ per cent, on October 28 it was $+44.5$ per cent. When seen on March 6, 1937, the pulse was 92 and there was definite exophthalmos of the left eye, and marked tremor. Operation was advised, and a thyroidectomy was performed on April 5, 1937.

Comment Patients 10 and 11, given prolonged treatment with thyrotropic hormone, were not benefited. Patient 12, given three courses of thyrotropic injections, each of a month's duration, at intervals of two months, was not controlled. Patient 9 gradually improved, as will some cases on iodine alone. Patient 8, in whom the disease very gradually and spontaneously subsided, apparently developed non-responsiveness to thyrotropic hormone as the disease regressed, in contrast to patient 11 who was still responsive after nine months of injections, when the disease was progressive.

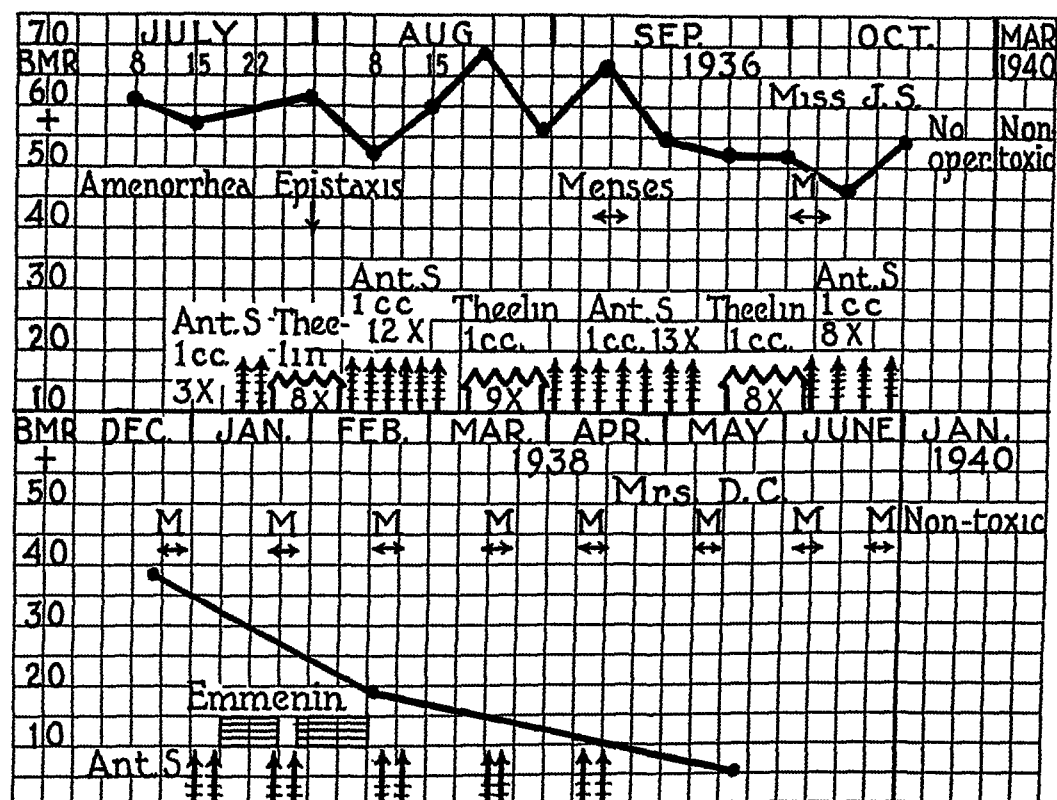
V The Effect of Ovarian and APL Hormone Injections

Three examples of the effect of ovarian and anterior pituitary-like hormone therapy may be given as a commentary on earlier results (Starr and Patton, 1935)

Case 13. Miss J S, aged 19 years Thyrotoxicosis was severe but of only four months' duration, weight loss from 128 to 107 pounds, pulse 130, lid-lag present, bruit over an enlarged, symmetrical thyroid, menses diminished and delayed Figure 13 indicates therapy with antuitrin-S (100 R U per c c) and theelin-in-oil (2000 I U per c c) Theelin was given before, and antuitrin-S during and following menses After three months of this treatment she had regained 23 pounds but was still toxic, the bruit persisted, tremor was present, the pulse was 110 She then left the city to take care of an invalid parent No operation was done She returned 16 months later without thyrotoxic complaints, weight sustained, pulse 88, and no eye signs

Comment Antuitrin-S and theelin-in-oil were without immediate effect but may have induced a gradual remission

Case 14 Mrs D C, aged 39 years, came to the clinic presenting all classical evidences of acute hyperthyroidism of nine months' duration Monthly treatment with antuitrin-S (100 R U daily for six days) timed to follow the first day of the menstrual cycle for five months, and interval ingestion of Emmenin (240 day oral units) for two months were associated with a gain of 20 pounds in weight and a remission of symptoms which has persisted now for two years



FIGS 13 and 14 Two examples of subsidence of hyperthyroidism following treatment with chorionic gonadotropin and estrogenic substance

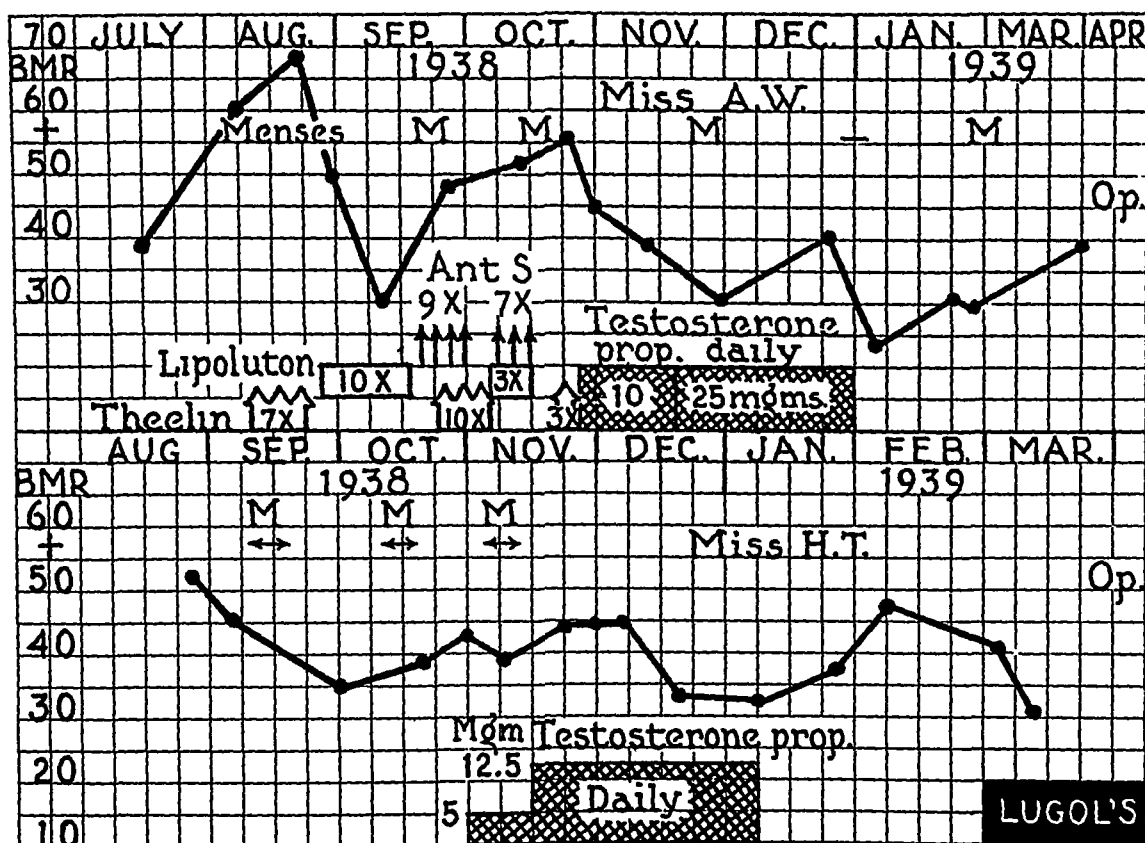
Case 15 Miss A. W., aged 30 years, came to the clinic in July 1938. She had a family history which included thyrotoxicosis in a sister, and a personal history of a previous attack of hyperthyroidism. She had a visible goiter, slight stare, a pulse rate of 128, and a basal metabolic rate of $+38$ per cent. Antithym-S (500 R U per c.c.), Lipoluton (2 rabbit units per c.c.) and theelin-in-oil (10,000 I U per c.c.) were given successively as indicated in figure 15, from early August to late October, over two menstrual cycles, without benefit.

Comment It may thus be seen that one of these three cases promptly improved during this type of treatment.

VI The Effect of Testosterone Propionate on Hyperthyroidism

Sir Levy Simpson reported beneficial action from male sex hormone in hyperthyroidism. This had been suggested by the comparative infrequency of this disease in the male. Our experience is that it is without effect.

Case 15 Testosterone propionate (see figure 15) was given hypodermically to Miss A. W. for two months following the unsuccessful ovarian therapy. At the initiation of the androgen treatment the basal metabolic rate was $+44$ per cent and after two months it was $+41$ per cent. Menstruation in December was absent. After discontinuing the male sex hormone, menstruation returned and a temporary depression of metabolic rate did occur. Successful thyroidectomy was subsequently performed.



FIGS 15 and 16 (Cases 15 and 16) Failure of treatment with male sex hormone to influence clinical course of hyperthyroidism in two young women

Case 16 Miss H T, aged 29 years, came to the clinic on August 19, 1938, with a fairly well established exophthalmic goiter and a basal metabolic rate of +53 per cent. A second control metabolic rate on September 3 was +42 per cent. On a high caloric diet, phenobarbital, and bed rest she gained weight, but her other symptoms failed to improve. On October 25 Perandien, 10 mg every other day for 10 injections, was given, the dose was then increased to 25 mg every other day for 34 injections, the last on December 30, 1938. There was a steady gain in weight and slight improvement in the subjective symptoms, but the basal metabolic rate fluctuated between +34 and +43 per cent and the pulse between 92 and 96, and on February 28, 1939, she was placed on Lugol's solution and prepared for thyroidectomy.

Case 17 Mr J S, aged 34 years, single, had an attack of hyperthyroidism in 1929, for which a thyroidectomy was done. Following the operation, nervousness and fatigue persisted until 1931. For six years he felt fairly well but then began to have attacks of diarrhea associated, since 1938, with nervousness, fatigue and nausea. On September 27, 1938, he presented symptoms of a mild hyperthyroidism, with a basal metabolic rate of +20 per cent and a pulse of 120. He had been taking iodine before coming to the clinic, this was stopped on admission and he was placed on phenobarbital, $\frac{1}{2}$ grain three times a day, and a high caloric diet. The basal metabolic rate rose to +38 and +36 per cent and the symptoms became aggravated. On November 1 testosterone propionate, 10 mg three times a week, was added to the above régime. On November 29 he reported that he felt better although he was still weak. The testosterone dosage was then increased to 25 mg three times a week, these injections were continued until January 3, 1939, by which time he had received 12 injections of 10 mg and 8 injections of 25 mg (see figure 17). All injections were then discontinued, the only medication being phenobarbital and cod-liver oil. The basal metabolic rate continued to fluctuate between +17 and +30 per cent and he was still weak and nervous. Accordingly, on February 28 he was placed on Lugol's solution and prepared for thyroidectomy.

VII *Vitamin A in Hyperthyroidism*

The relationship of vitamin A to the thyroid gland and its hormone, thyroxin, has recently attracted a great deal of attention. Many investigators, both in the United States and on the Continent, have devoted much time, energy and ingenuity to the study of this problem. All of these studies point to the existence of an antagonism, chemical or physiologic in nature, between vitamin A and thyroxin. Almost all the effects of the latter are counter-balanced and neutralized by the former and vice versa, the intoxication of the animal produced by the feeding of enormous doses of vitamin A can be prevented by the simultaneous feeding of thyroxin.

How far this finding is applicable to human hyperthyroidism is problematic. Several prominent German clinicians, such as Wendt, Falta, and Dietrich, have treated Graves' disease with huge doses of vitamin A in the form of a special German preparation, "Vogan." They report excellent results in the majority of their cases—gain in weight, lowering of the basal metabolic rate, slowing of the pulse, and general improvement in subjective symptoms. Unfortunately, their cases were poorly controlled. We are presenting here a case of recurrent Graves' disease in which we used even

larger doses of vitamin A than the German clinicians, in the form of a specially purified cod-liver oil furnished to us by the Abbott Laboratories.*

Case 18 Mrs H B, aged 49 years, a widow, had had an attack of toxic goiter in 1932, which gradually subsided. In 1935, after the death of her husband, symptoms recurred in a much aggravated form, and she was subjected to thyroidectomy. For about a year after the operation her general condition continued to improve although she was unable to gain weight. Late in 1936 she developed hot flashes with a recurrence and aggravation of all her thyroid symptoms. When first seen at the clinic in

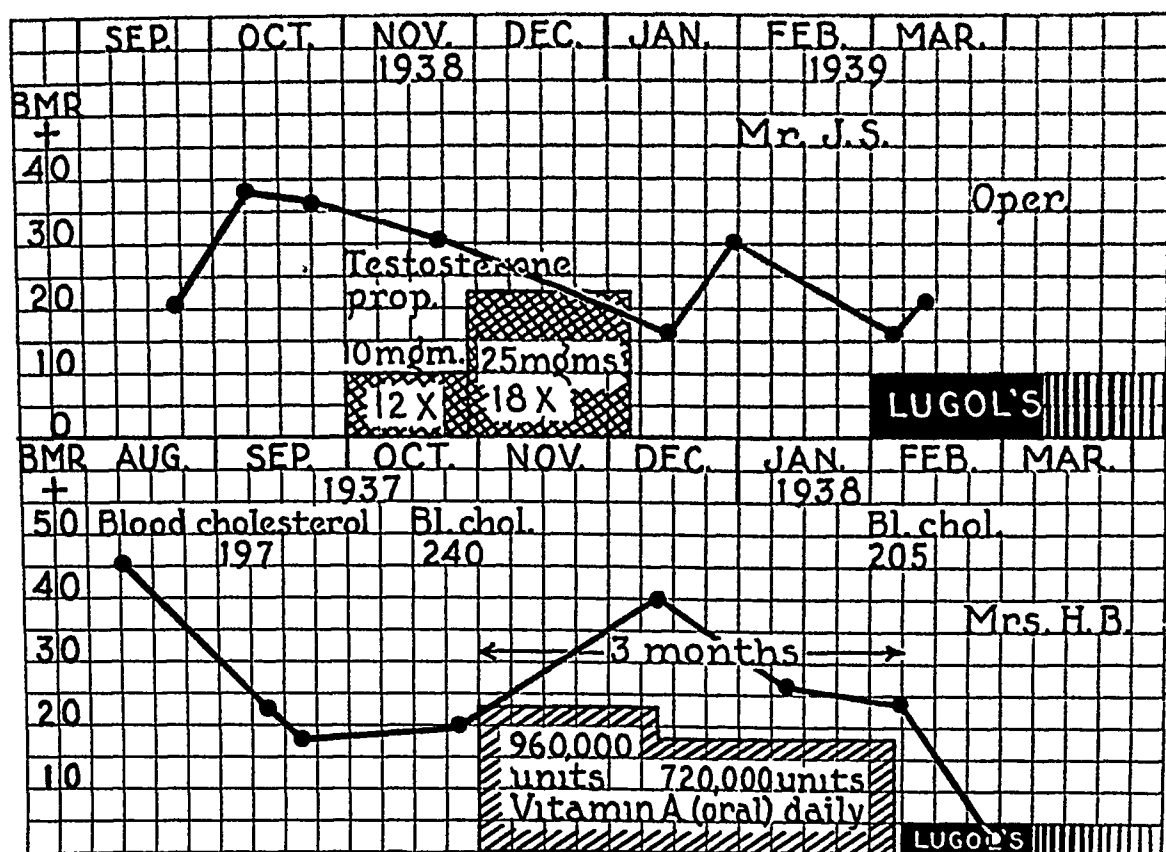


FIG 17 (Case 17) Mr J S Failure of testosterone to modify course of hyperthyroidism in a male patient

FIG 18 (Case 18) Mrs H B Massive dosage of oral vitamin A for three months without effect on clinical course of hyperthyroidism

May 1937 she had a pulse of 114, a basal metabolic rate of + 50 per cent, enlargement of the right lobe of the thyroid and marked stare. She was placed on phenobarbital, 2 grains daily, and a high caloric diet, this was continued from May 11 to June 29. The response was poor. On June 24 the pulse was 112, and the basal metabolic rate + 33 per cent, she had gained no weight and was still very nervous and tremulous. On June 29 she was placed on theelin, 1 c c daily, which was continued until August 9, without any benefit, on that date her pulse was 120, the metabolic rate + 46.5 per cent, her weight had increased from 111 to 118 pounds. She was again given a high caloric diet, karo syrup sandwiches, and phenobarbital. For a while she felt better, and gained another pound or two, the metabolic rate decreased to an average + 21.2 per

* We wish to thank Dr Carl Nielsen of the Abbott Laboratories for his generous supply of vitamin A concentrate

cent However, on November 2 she became worse, complaining of insomnia, extreme nervousness and irritability, heat intolerance, excessive perspiration, and diarrhea She was then placed on vitamin A, 960,000 I U daily by mouth This was continued throughout November, December, January (1938) and until February 8, the response was very slight, there was very little gain in weight (120 to 122 pounds), the pulse was only slightly reduced (100-96), and the basal metabolic rate was +40.5 per cent on December 9, +26.2 per cent on January 11, and +23 per cent on February 8 There was, however, considerable improvement in her subjective symptoms The vitamin A was discontinued on February 8, and she was placed on Lugol's solution in preparation for surgery, the metabolic rate dropped to +3 per cent in two weeks A thyroidectomy was performed on June 8, 1938

In comparing this case with those reported in the German literature it is especially interesting to note the blood cholesterol findings in this patient The German clinicians stressed particularly the rise of the blood cholesterol and the consequent considerable gain in weight in their patients in response to the vitamin A treatment We failed to find such a rise, in fact, we found a decrease in the blood cholesterol Before the initiation of the vitamin A treatment, when our patient was receiving only phenobarbital and a high caloric diet, the blood cholesterol rose from 197 mg on June 22, 1937 to 240.5 mg on November 2, while after three months' treatment with vitamin A the cholesterol declined to 205 mg on February 7, 1938

VIII *Vitamin C in Hyperthyroidism*

There are a great many conflicting reports concerning the relationship of vitamin C to the thyroid Some investigators claim to have found hyperactive and hypertrophied thyroids in animals (guinea-pigs) that have been kept on a vitamin C-free diet, and further claim that they have been able to prevent the hyperthyroidism ordinarily produced by thyrotropic hormone injections by the simultaneous feeding of vitamin C They contend, therefore, that vitamin C has a specific antithyrotropic effect which it exerts upon the thyroid All of these claims are countered by another group of observers who have used the measurements of the cell heights as a criterion and who claim that the cell height of the thyroid of scorbutic animals is so slightly changed that one is not entitled to speak of a hyperactive thyroid Similarly, they have been unable to inhibit the effects of thyrotropic hormone upon the thyroid even by huge doses of vitamin C

In the case presented here we have attempted to determine the effects of huge doses of vitamin C upon the basal metabolic rate, blood cholesterol and weight curve of human hyperthyroidism, we also wished to ascertain whether the rise in blood vitamin C and in urinary and fecal vitamin C excretion, which always follows the ingestion of such huge quantities of vitamin C would be offset by the hyperactive thyroid We are grateful to Professor Chester Farmer of the Department of Chemistry, Northwestern University Medical School, who provided ascorbic acid and carried out chemical determinations

Case 19. Mrs. J. R., aged 30 years, gravida 7, para 1, youngest child six months old. After the birth of her second child four years previously she had a so-called "nervous breakdown"—probably acute hyperthyroidism—with loss of weight from 125 to 89 pounds, followed by gradual recovery in 18 months. It should be noted that two completed pregnancies occurred after this illness. Symptoms of hyperthyroidism began again during this last puerperium. The baby was weaned at four months with return of menses, but in contrast to Case 1 the hyperthyroidism was not abated. On examination she had a pulse of 120, marked tremor, lid-lag, flushing and sweating. After two months' observation the basal metabolic rate determination averaged about +33 per cent. Three grams of cevitamic acid were given by mouth daily in divided doses for a month, with two short interruptions as indicated in figure 19. Blood cevitamic acid level rose from 0.25 mg per cent to a peak of 2.5 mg per cent, but maintained a concentration of 1.75 mg per cent. From 1000 to 1400 mg were measured per 24 hours in the urine. Fecal assays were negligible. No amelioration of hyperthyroidism or reduction of the basal metabolic rate occurred. Thyroidectomy was successfully performed on July 27, 1939.

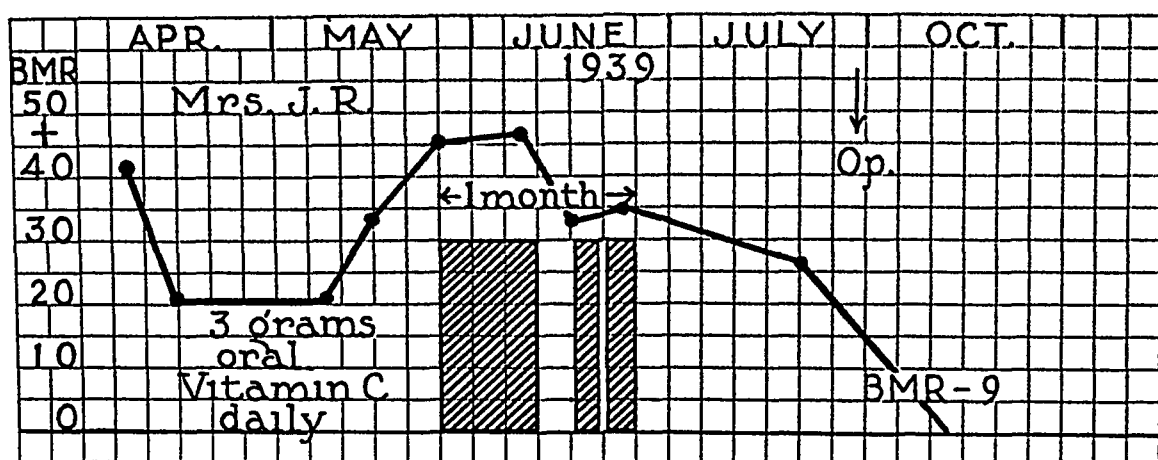


FIG 19 (Case 19) Mrs. J. R. Massive oral medication of vitamin C for one month without effect on basal metabolic rate in hyperthyroidism

SUMMARY

Abrupt and complete subsidence of acute hyperthyroidism in a young mother occurred when she weaned her baby (figure 1). The cure of a girl during adolescence, coincident with injections of chorionic gonadotropin and aqueous estrogenic substance, was very similar (figure 2). Desiccated thyroid was given to five patients, it was combined with Lugol's solution in three of these (figures 3, 4 and 7) without benefit, 5 grains a day alone failed to raise the rate in one case (figure 5), in another case (figure 6) the rate subsided rapidly but exophthalmos increased.

Thyrotropic hormone in one patient was calorogenic during one phase of the disease (figure 8) but apparently without effect two years later when the hyperthyroidism was milder. In four patients who were given prolonged treatment with thyrotropic hormone and Lugol's solution, no remission was induced (figures 9, 10, 11 and 12). One of these patients remained sensitive to the thyrotropic action after 10 months of intermittent treatment. This

suggests that development of an antihormone or antibody in this patient did not occur. Two patients treated with chorionic gonadotropin became non-toxic (figures 13 and 14). Two young women and one man with hyperthyroidism (figures 15, 16 and 17) were not improved by testosterone propionate. One patient was treated with very high dosage of vitamin A (figure 18) with no effect on the metabolic rate which was then promptly reduced by Lugol's solution. Massive dosage of vitamin C was likewise without effect on the metabolic rate in another patient (figure 19).

CONCLUSION

The existence of a chalone mechanism acting to restore thyroid activity to normal is suggested by known physiological equilibria. An occasional case of hyperthyroidism subsides rapidly as though such a mechanism were in operation. Attempts to induce such a chalone by administration of desiccated thyroid, thyrotropic hormone, vitamin A, vitamin C and testosterone propionate, have been ineffective. Treatment with chorionic gonadotropin has been accompanied by remission of hyperthyroidism in a number of cases.

REFERENCES

- STARR, PAUL. Clinical studies with thyrotropic pituitary hormone, *Proc Soc Exper Biol and Med*, 1935, **XXXIII**, 462-464.
- STARR, PAUL, and PATTON, HELEN. Studies of variations in individual human response to thyrotropic hormone preparations, *Ann Trans Am Assoc for the Study of Goiter* (in press), *West Jr Surg*.
- STARR, PAUL, and PATTON, HELEN. Observations of remissions in hyperthyroidism induced by pregnancy urine extract, *ANN INT MED*, 1935, **VIII**, 825-833.
- KUNDE, M. M. Studies on metabolism experimental hyperthyroidism, *Am Jr Physiol*, 1927, **LXXII**, 195-215.
- KUSCHINSKY, G. Über die Bedingungen der Sekretion des Thyreotropen Hormons der Hypophyse, *Arch f exper Path u Pharmacol*, 1933, **CLX**, 510-533.
- STARR, PAUL. Course of hyperthyroidism under iodine medication, *Arch Int Med*, 1927, **XXXIX**, 520-535.
- LEVY SIMPSON, S. Value of testosterone propionate in hyperthyroidism, *Postgrad Med Jr*, 1938, **IV**, 144-146.

ACUTE HEPATITIS OF ALCOHOLISM: A CLINICAL AND LABORATORY STUDY *

By HORACE B. CATIS, M.D., *Los Angeles, California*

In an earlier study several liver function tests were carried out upon patients in whom a diagnosis of cirrhosis had been previously confirmed, both by peritoneoscopy and liver biopsy. The excretion of bromsulfalein was found to be the most accurate test to measure the degree of liver damage.¹ This opinion is in accordance with the experience of other workers.^{2, 3} However, the pathological diagnosis and the estimate of liver function are not always in agreement because some patients, having a high retention of bromsulfalein, die of subacute cirrhosis before marked atrophy occurs; others may survive until marked atrophy of the liver parenchyma has taken place. Furthermore, satisfactory bromsulfalein excretion may occur although the organ is in a state of extensive fibrosis. From an analysis of the causes of death, whether due to pneumonia, gastrointestinal hemorrhage, or liver insufficiency, it appeared that those having either early or advanced cirrhosis died of the same immediate causes in relatively the same proportions. Nevertheless, the bromsulfalein excretion test was of definite value in detecting liver damage, and it disclosed that some acute alcoholics, without jaundice, peripheral neuritis, or a palpable liver, were found to retain an abnormal amount of the dye at the end of half an hour.

The purpose of this study was to determine, by repeated testing of those alcoholics who had an initial dye retention, the time necessary for the liver function to return to normal. In previous studies it was found that those who had been drinking for less than two weeks failed to show abnormal bromsulfalein tests. The high caloric content of alcoholic beverages, particularly fortified wines, automatically reduced food consumption to meager amounts. Because these patients imbibed alcohol they did not wish to eat and, therefore, after a period of time suffered a depletion of the liver's protein, carbohydrate, and vitamin reserves, thus leaving the organ susceptible to injury. This sequence of events has been experimentally demonstrated in animals, and it is inferred that it occurs in men. For instance, Goldschmidt, Vars, and Ravdin⁴ tested the protective value of different food-stuffs fed to chloroformed mice. They showed that a high protein diet was definitely protective, and served to minimize the destructive action of hepatic toxins. The value of carbohydrate feeding seems to be its rôle of protein sparing, leaving proteins to neutralize the toxic action of chloroform. Messenger and Hawkins⁵ maintain that a high protein diet protects dogs against liver injury from large doses of arsphenamine. Finally, rabbits fed on a

* Received for publication September 4, 1940

From the Department of Medicine, The University of Southern California School of Medicine, and The Los Angeles County Hospital

balanced diet, with the exception of some components of yeast, were observed by Rich and Hamilton⁶ to develop a cirrhosis resembling Laennec's cirrhosis in man. It is not surprising therefore that a certain number of the poorly nourished alcoholics whom we investigated were found to suffer from hepatitis, although in the majority of them the liver injury was not sufficiently marked to be clinically recognizable.

There is apparently a relationship between the increased admissions to the Los Angeles County Hospital of patients with cirrhosis, and the repeal of prohibition. Evans and Gray⁷ found among 17,879 autopsies performed

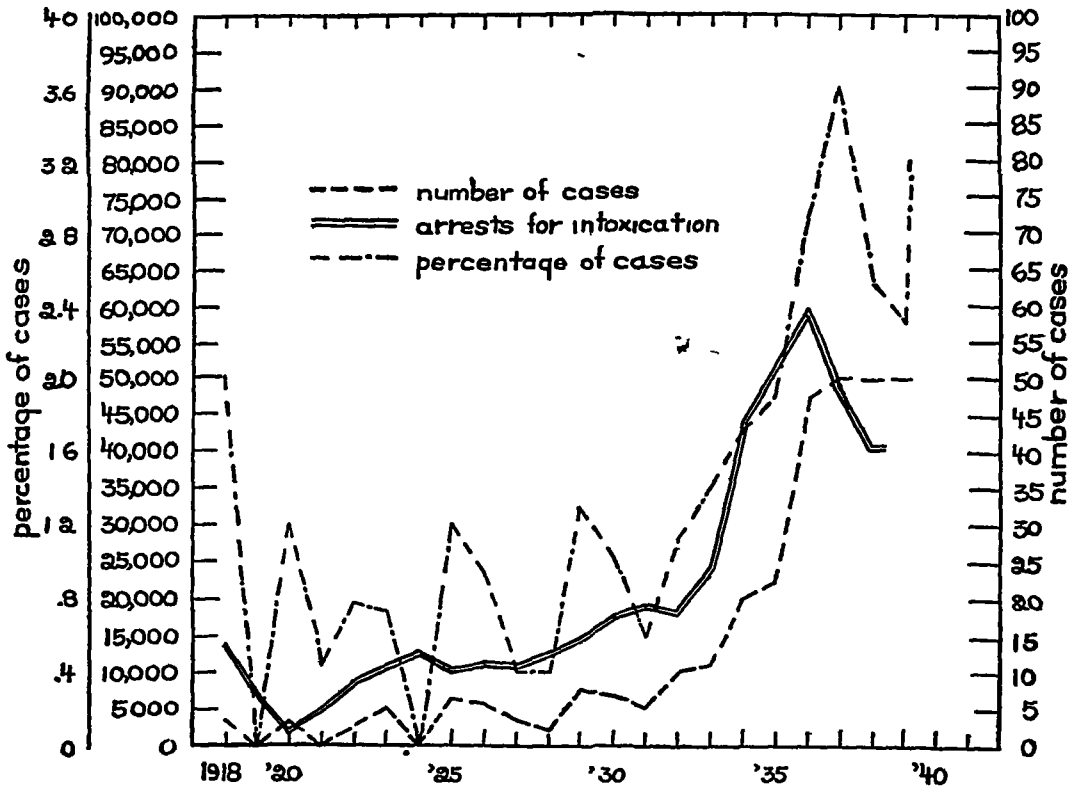


CHART 1 Represents the relationship between the number of arrests by thousands in the City of Los Angeles and the incidence and percentage of all cases having postmortem evidence of alcoholism from one and one-half to three years before death. The blood Wassermann reaction was negative in all cases, and the blood Wassermann reaction showing 10 per cent dye retention, and 1937, 217 examination in the retention (cl

PROCEDURE

The selection of alcoholic patients was not made at random, since the objective was to isolate those who had a dye retention. The patients were then rechecked at intervals until the retention had disappeared. The ones selected were shaky and on the verge of delirium tremens. They had been drinking for not less than two weeks and some had been drinking steadily for six weeks. The determination was done according to the following technique. The amount of bromsulfalein injected intravenously was 5 mg per kilogram of body weight, and a blood sample was withdrawn exactly 30 minutes later. The blood specimen was poured into an oxalated receptacle and centrifuged. A measured amount of serum was removed, diluted with an equal amount of acetone, shaken, and again centrifuged. After alkalinizing, the specimen was checked by the colorimetric method and the reading was multiplied by two.

RESULTS

The present study represents a total of 40 bromsulfalein tests made on 25 alcoholics. Fourteen of the men were found to retain 5 per cent or more on the first test, and were regarded as having a disturbance of liver function. Of these 14 patients, one had 30 per cent, five had 20 per cent, and eight had from 16 per cent to 5 per cent dye retention. Six of the patients were followed with interval testing until the dye test returned to normal. The other patients could not be followed because they left the hospital before their liver function tests had returned to normal.

The following brief abstracts of three of the cases illustrate some of the clinical aspects of alcoholics with a temporary retention of bromsulfalein.

CASE REPORTS

Case 1 J. B., white, 32 years old, had been previously admitted to the hospital on November 15 for the removal of an epithelioma of the face. A positive blood Wassermann reaction was obtained. He had been drinking steadily for six weeks. One week before his arrest had suffered from nausea and attacks of vomiting. Because of a mild diarrhea and complained of, did not wish to eat. For three days after he had no icterus, nor was there any tenderness in the epigastrium. There was no loss of vitamin reserves, thus leaving aching pain in the legs on pressure. The bromsulfalein test was done, 20 per cent of the dye was retained, and four days later the results of the test were unchanged (chart 2, J. B.). On February 16, one week after he was first seen, peritoneoscopic examination and liver biopsy were done by Dr. John Ruddock. The preoperative diagnosis was alcoholic hepatitis. The report was as follows: "No peritoneal fluid was seen, all visceral surfaces appeared normal. Gall bladder and appendix were normal. The liver was slightly enlarged, its edge is sharp." Conclusion: no pathologic changes seen. Examination of the liver biopsy tissue showed that the hepatic architecture was slightly disturbed. The periportal connective tissue was only very moderately increased, if at all. The amount of fat in the liver was more abundant in the

centers of the lobules (figure 1) There was a mild inflammatory change in the liver as evidenced by the moderate number of mononuclear cells and an occasional polymorphonuclear leukocyte in the periportal connective tissue. An occasional necrotic liver cell was seen and a considerable variation in the size of the liver cell nuclei, with many of them appearing rather large and deeply stained. The diagnosis was "Mild toxic hepatitis and fatty liver." Eight days following peritoneoscopy another bromsulfalein test was done which was normal.

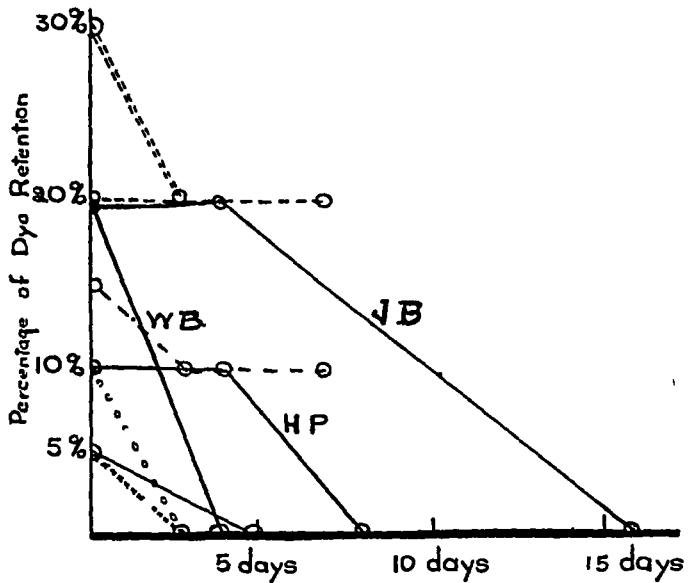


CHART 2 Follow-up by means of the bromsulfalein liver function test upon alcoholics having a half-hour retention

In this case there was evident correlation between the pathological interpretation and the bromsulfalein test. Liver damage was present and was associated with physiological dysfunction, since the reticulo-endothelial cells were unable to rid the blood stream of the dye.⁸

Case 2 H P, white, 55 years old, for five weeks prior to admission had drunk from one and one-half to two quarts of wine daily. When first seen, March 10, 1940, the blood Wassermann reaction was negative. His bromsulfalein test was reported as showing 10 per cent dye retention, and when repeated four days later was again found to show 10 per cent retention (chart 2, H P). Peritoneoscopy was done by Dr. John Ruddock, March 14, and the following notes were made: "The liver edge below costal border. There was no edema, and no fluid. The liver was in color and of usual size, its peritoneal surface was smooth. There were no adhesions around the cecum. Impression: Grossly normal liver." Examination of a liver biopsy revealed normal findings. Three days later the dye test was normal.

In this particular instance there is a lack of agreement between the pathological findings and the results of the liver function tests. Only mild toxic dye retention test was present the same day that pathological findings indicating definite impaired physiologic function, liver tests are regarded as normal were observed. Undoubtedly there may be a certain number of this

acute alcoholism that the serum bilirubin concentration ranged from 0.85 to 2.1 units, and in five patients he observed abnormal urobilinogen concentration which ranged from dilutions of 1:90 to 1:350. The one patient in this group who was most toxic became well, according to the results of the tests, after a period of five days. After a preliminary two-day fasting period, MacNider¹⁰ subjected dogs to either a 12- or 24-hour period of severe alcoholic intoxication and found evidence of lobular damage to the liver. At the end of 12 hours the liver was pale and the lobulations were not distinct. Microscopic examination revealed marked edema of the liver cells in the peripheral half of the lobules and accumulations of stainable lipid material. MacNider noted that the nuclei in the peripheral portions were hypochromatic. Sections of the liver of the 24-hour intoxicated dogs contained evidence of edema involving the entire lobule, which was most intense in the outer zone. The capillary spaces were obliterated and the central veins compressed. Grossly the organ was enlarged and grayish-white in color. The livers of control dogs which had been deprived of food for two days and then given an ether anesthesia for three hours were found by microscopic examination to contain small drops of lipid substances in the periphery of the lobule. When liver function was tested with phenoltetrachlorophthalein, the dogs which had been subjected to a 12-hour intoxication were found to retain from 7 to 10 per cent of the dye at the end of one hour during the first day, but had no retention when tested on the third day. Dogs that had been intoxicated for 24 hours were found to retain from 14 to 17 per cent of the dye, and on the third day the test became negative.

The experimental investigation cited above indicates that liver damage as revealed by the dye retention test may occur from alcohol and anesthetic administration, and may disappear if the damage is not too severe. The results of this study also emphasize that the bromsulfalein liver function test is sensitive enough to pick up various degrees of liver damage, either with physiologic dysfunction alone or associated with definite pathological changes. Not all alcoholics show such liver dysfunction, but only about one out of every 300 of the cases which were observed during the course of this investigation.

CONCLUSIONS

1. Some alcoholics after prolonged and continuous drinking have liver impairment as shown by the bromsulfalein test.

2. The earliest discernible change in the livers of such patients is a decrease in the physiological efficiency of the reticulo-endothelial cells which remove the dye from the circulation. Biopsy made in two cases showed no pathological disturbance in one, and in the other evidence of only mild toxic hepatitis with fatty infiltration, although dye retention was present in both.

3. The 25 alcoholics who had abnormal bromsulfalein tests are regarded as being cases of hepatitis unrecognized clinically. A certain number of this

group have a progressive liver deterioration leading eventually to Laennec's cirrhosis

BIBLIOGRAPHY

- 1 CATTS, H. B. Relation of liver function to cirrhosis of liver and to alcoholism, *Arch. Int. Med.*, 1941, **LXVI**, 383-398
- 2 SOFIER, L. F. Present day status of liver function tests, *Medicine*, 1935, **XIV**, 185-254
- 3 MAGATH, T. B. Takata-Ara test of liver function, *Am. Jr. Digest Dis. and Nutr.*, 1936, **II**, 713-716
- 4 GOLDSCHMIDT, S., VARS, H. M., and RABIN, I. S. The influence of foodstuffs upon the susceptibility of the liver to injury by chloroform, and the probable mechanism of their action, *Jr. Clin. Invest.*, 1939, **XXIII**, 277-289
- 5 MESSINGER, W. J., and HAWKINS, W. B. Arsphenamine liver injury modified by diet, *Am. Jr. Med. Sci.*, 1940, **CXCIX**, 216-225
- 6 RICH, A. R., and HAMILTON, J. D. The experimental production of cirrhosis of the liver by means of a deficient diet, *Bull. Johns Hopkins Hosp.*, 1940, **LXVI**, 185-198
- 7 EVANS, N., and GRAY, P. A. Laennec's cirrhosis report of 217 cases, *Jr. Am. Med. Assoc.*, 1938, **CX**, 1159-1161
- 8 MILLS, M. A., and DRAGSTADT, C. A. Bromsulfalein dye retention test as a measure of functional activity of reticulo-endothelial system, *Proc. Soc. Exper. Biol. and Med.*, 1936, **XXXIV**, 228-231
- 9 WALLACE, R. P. Liver injury in acute alcoholic poisoning, *Proc. Soc. Exper. Biol. and Med.*, 1927, **XXIV**, 598-599
- 10 MACNIDER, WM. DE B. Acute degenerative changes and the changes of recuperation occurring in the liver from the use of ethyl alcohol, *Jr. Pharmacol. and Exper. Therap.*, 1933, **XLIX**, 100-116

THE SIGMOIDOSCOPIC DIAGNOSIS OF PERIARTERITIS NODOSA^{*} †

By JOSEPH FELSEN, M D, *New York, N Y*

THE diagnosis of periarteritis nodosa during life is difficult. Since the classical descriptions of the disease by Rokitsansky in 1852 and Kussmaul and Maier in 1856 more than 200 cases have been reported, but relatively few of these were diagnosed intra vitam (31 cases up to the end of 1935)¹. The purpose of the present communication is to report one such case in which the diagnosis was definitely established by sigmoidoscopy and confirmatory evidence obtained at necropsy. Two additional cases of relevant interest will also be described because they provided excellent clinical and pathological material for a better understanding of our observations at sigmoidoscopy. Detailed laboratory findings are given where they appear to be of interest in connection with the underlying clinical and pathological condition.

Case 1 C D, female, aged 45 years, was admitted to The Bronx Hospital on February 16, 1936, with a history of asthma following an upper respiratory infection in September 1935. A physician informed her that a skin test had revealed a sensitivity to dust. Two weeks before admission the patient contracted another "cold" with aggravation of her asthma. Physical examination revealed an emphysematous chest and the presence of sibilant and sonorous râles. Skin tests revealed a slight reaction to dust, oak and birch. A polypoid mass was seen blocking the right nasal meatus and there was a pan-sinusitis on the same side. On March 4 the antrum was punctured, but no pus obtained.

Laboratory examinations were as follows. The blood Wassermann and Kahn tests were negative. A blood count on February 17 revealed hemoglobin 86 per cent, erythrocytes 5,400,000 per cu mm, leukocytes 38,400 per cu mm, polymorphonuclear neutrophils 83 per cent, band forms 6 per cent, lymphocytes 9 per cent, monocytes 2 per cent. Blood chemical tests were normal on the same day. The sputum was slightly blood-tinged on February 20, but otherwise not abnormal. The bleeding time was 2 minutes and coagulation time 4 minutes. On March 4 the leukocytes were 11,500 per cu mm, polymorphonuclear neutrophils 76 per cent, band forms 4 per cent and lymphocytes 20 per cent. On February 19 roentgenogram of the chest showed coarse infiltration of both lower lobes with small confluent patches. The appearance was that of chronic inflammatory disease with a superimposed bronchopneumonia (Dr Snow). On February 21 roentgenographic examination showed clouding of the right frontal ethmoidal sinuses and antrum. On March 5 there was noted a partial clearing of the lung in both lower lobes.

* Received for publication December 16, 1939.

From the Department of Laboratories and Research, The Bronx Hospital, New York, N Y.

† I am indebted to Dr Emil Koffler and Dr Alexander Goldman, The Bronx Hospital, for the privilege of studying cases 1 and 2, to Dr Ephraim Bluestone, Dr David Perla (Montefiore Hospital), Dr K M Bowman (Bellevue Hospital), Dr George Baehr and Dr Paul Klemperer (Mt Sinai Hospital) for the follow-up studies and pathological material in case 1. I also wish to acknowledge the kindness of Dr Henry Greenberg for the clinical data from Fordham Hospital in case 2 and that of Dr Benjamin F Sandler and Dr Joseph Ehrlich for making available the clinical and pathological material in case 3.

The temperature ranged from 99 to 102° F for approximately one week after admission, following which it fell to normal. The patient was discharged on March 8, 1936 and re-admitted on April 27. Her asthma had continued unabated and the patient lost 18 lbs in weight. The blood pressure on admission was 150 mm systolic, 92 mm diastolic. She was considerably more distressed and orthopneic than on her previous admission. Adrenalin administered intravenously provided considerably more relief than when given subcutaneously. The asthmatic paroxysms subsided somewhat. On May 21 the fundus examination revealed no disease changes. On May 26 the patient complained of precordial pain.

Laboratory examinations were as follows. Examination of eight specimens of urine revealed an occasional erythrocyte and trace of albumin, as had been previously found during her first admission. The blood counts were:

Date	Hgb	RBC	WBC	PN	Eos	SL	Misc
4-27	82%	4,500,000	15,900	51	15	32	2
5-11	69%	4,100,000	25,200	85	1	6	8
5-25	79%	4,500,000	13,800	72		24	4

The blood calcium on May 4 was 11.1 and phosphorus 3.4 mg per 100 c.c. Platelets on May 14 were 210,000 per cu. mm., bleeding time 1 minute 30 seconds, coagulation time 2 minutes, 30 seconds. Roentgenographic examination of the chest on May 2 suggested a chronic pneumonitis of both lower lobes. This was corroborated on May 13. On June 3 an electrocardiogram revealed a possible coronary occlusion.

Except for a temperature of 102° to 104° F during the period from May 10 to May 15, the clinical course was practically afebrile. The pulse varied from 90 to 130. The patient was discharged on June 5, 1936, and re-admitted on August 22 with a complaint of loss of weight, weakness and wasting of both hands and abdominal pain. For three or four days before admission, diarrhea had been present. The patient appeared chronically ill and asthmatic. There was some weakness of the left upper extremity and tremor of the hands. Spastic intestine was felt in the left and right lower quadrants of the abdomen. The blood pressure was 120 mm systolic, 80 mm diastolic. Pulsations were present in the arteries of both upper and lower extremities. There was considerable atrophy of the muscles of the hand.

Laboratory examinations were as follows:

Blood counts

Date	Hgb	RBC	WBC	PN	Eos	SL	Other Forms
8-24	80%	4,100,000	32,600	24	68	3	5
8-26			31,800	12	70	8	10
9-10			23,000	32	56	8	4
10-1	83%	4,400,000	22,200	34	52	10	4

Five urine examinations showed a trace of albumin in two specimens. Biopsy of the deltoid muscle revealed hyalinized striated muscle, but no evidence of periarteritis nodosa. Roentgenographic examination of the gall-bladder with dye failed to outline the organ. There was some enlargement of the liver. A barium enema study of the colon proved negative. The patient ran an afebrile course and was discharged on August 22.

Opportunities were afforded for repeated sigmoidoscopic studies at The Bronx Hospital and, after her discharge, at a nursing home and at the patient's residence. At the first examination the findings were unlike any picture previously encountered by us in any patient. In the rectosigmoid there were peculiar horizontal,



FIG 1 Intestine in case 1 Arrows point to focal and linear thromboses in the vessels of the mesentery Note the segmental type of involvement and continuation of the lesions into the intramural branches of the intestinal wall (above upper arrow and to the left of lower arrow) Picture taken as a transparency (approximately $\times \frac{1}{2}$)

red streaks running in parallel lines, each approximately 1.5 cm in length and separated by approximately 1 cm of healthy mucosa. Direct pressure by a blunt instrument did not obliterate the streaks nor did gentle swabbing wipe them away. Careful examination with a telescopic device and green filter placed the lesion *within* a vessel since the latter could be seen proximal to each streak and, with great difficulty visualized as a thin almost bloodless hairline distal to it. Between the proximal and distal points the vessel appeared to be bellied out quite uniformly and the obvious inference was that it represented a thrombosed artery. Since there were no petechiae or other evidence of subacute bacterial endocarditis, an embolic phenomenon could be ruled out with reasonable certainty. Moreover, we had never seen this picture in cases of subacute bacterial endocarditis. Two follow-up examinations revealed a persistence of the lesions above described and, in addition, a definite elevation of the mucosa over the affected vessels. This indicated that they were located in the sub-



FIG 2 Thickened, recanalized healed vessel in the intestinal submucosa, case 1

mucosa. Several small focal areas of thrombosis were also noted in the same as well as in previously unaffected vessels. Anatomically these corresponded to the end branches of the sigmoid and superior hemorrhoidal branches of the inferior mesenteric and middle hemorrhoidal branches of the internal iliac arteries. In places the appearance was distinctly segmental. The clinical symptomatology indicated involvement of larger, extramural arteries inasmuch as the collateral circulation within the bowel wall was sufficient to maintain an adequate blood supply. No necrosis or inflammation of the mucosa was seen so that the persistent cramps could not be adequately explained on that basis. Previous experience had also shown that in arteriosclerosis the small intramural arteries presented a characteristic tortuous or corkscrew appearance and, in the later stages, straight tapering or obliterated vessels. Section had revealed medial sclerosis and subintimal proliferation as the essential underlying pathology, but never thrombosis of the smaller intramural intestinal vessels. Correlated studies of the intestine in other cases of periarteritis nodosa in which the diagnosis had been proved at necropsy revealed lesions almost identical with those seen in our living patient and accordingly a diagnosis of periarteritis nodosa was made (probably stage 2 or 3 (inflammatory or granulation tissue stage) because of the high eosinophilia. In order to test the accuracy of these observations it was essential

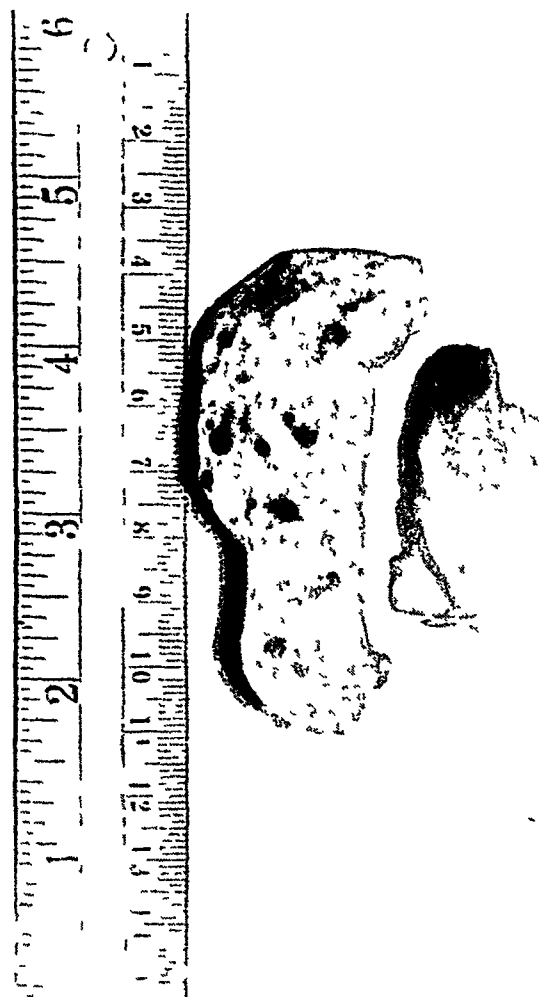


FIG 3 Section of kidney in case 2, showing multiple thrombosed vessels with aneurysmal formation (specimen at left) and massive hemorrhagic infarction (specimen at right)

follow up the patient through each of the three hospitals where the subsequent clinical and pathological studies were carried out

After a short stay at Montefiore Hospital the patient was transferred to the Psychiatric Division of Bellevue Hospital. Neurological examination revealed optic nerve atrophy and left wrist drop with sensory impairment. Spinal fluid examination was negative. The discharge diagnosis, three days after admission, was psychosis with somatic disease. The patient was then admitted to Mt Sinai Hospital on December 21, 1936, with a diagnosis of periarteritis nodosa as previously made at The Bronx Hospital. Physical examination revealed a poorly developed, pale, cachectic middle-aged female who was irrational and disoriented. There was moderate cyanosis of the lips and finger nails. The neck veins were engorged and several small hard nodules the size of millet seeds were noted on the right side of the forehead. Several small lymph nodes were felt in the posterior triangles of the neck, axillary, epitrochlear and inguinal regions. There was some dullness at the right base of the lung with numerous moist and crackling râles. Râles were also heard at the left base and anterior aspect of the upper part of the right chest. The heart was slightly enlarged



FIG 4 Mesenteric and intramural intestinal lesions in case 3. Note how in some of the focal mesenteric lesions the process appears to extend in a linear fashion (upper arrow). The typical intramural intestinal lesions, both focal and linear, are indicated by the two arrows at the right. Picture taken as a transparency (approximately normal size).

to the left, gallop rhythm was present and a pericardial systolic friction rub was heard at the lower left part of the sternum. The liver was smooth, tender to palpation and enlarged to a distance of two fingers'-breadth below the umbilicus. On the lateral aspect of the right knee there was noted a small cartilaginous-like movable nodule located in the subcutis. Another, somewhat softer, nodule was felt over the tenth dorsal vertebra. A small scar was seen in the left deltoid area (the site of a previous biopsy). There was slight edema of the ankles. Examination of the fundi revealed atrophy of the optic discs. The arteries were very narrow and a small hemorrhage was present above the right disc. Neurological study indicated median nerve paralysis involving the left hand with wrist drop. The interossei were wasted, the fingers being held in adduction with flexion of the proximal interphalangeal joints. The knee jerk was more active on the left than on the right side. Blood pressure was 150 mm systolic, 110 mm diastolic. The leukocytes were 19,250 per cu mm, blood glucose 75 mg, urea nitrogen 75 mg per 100 cc and carbon dioxide combining power 25 volumes per cent. The urine contained a trace of albumin and an occasional erythrocyte. The clinical course was rapidly downhill and the patient died on December 30, 1936, nine days after admission and approximately 16 months after the onset of illness.

The necropsy findings were as follows

- 1 Periarteritis nodosa involving the vessels of the kidneys, liver, mesentery, diaphragm, spleen, lungs and heart
- 2 Diffuse cortical scarring of both kidneys
- 3 Subcapsular atrophy and chronic passive congestion of the liver
- 4 Subacute suppurative pericarditis
- 5 Hypertrophy and dilatation of the right auricle and ventricle
- 6 Myocardial fibrosis
- 7 Thrombosis of the left auricular appendage
- 8 Generalized edema, ascites and bilateral hydrothorax
- 9 Bronchopneumonia of all lobes
- 10 Hemorrhagic infarct of the right lower lobe
- 11 Marked pulmonary edema and congestion

The causes of death were bronchopneumonia and cardiac failure

Examination of the gross intestinal material borrowed for pathological study included only portions of the small intestine with attached mesentery. Marked involvement of the mesenteric vascular loops and straight vessels was present. There were nodular, linear and "skip" or segmental lesions. The latter were readily visible in the straight vessels coursing through the mesentery from the loops to the intestinal wall. The linear areas of involvement presented themselves as thickened vessels with parallel sides projecting slightly above the general surface level of the mesentery. The nodular lesions were focal and appeared to spread beyond the confines of the vessel wall. In some places the pathologic changes involved a loop as well as the proximal portions of the branches leading away from it. In others, there were small "spotty" focal lesions in the mesentery followed by a linear intramural lesion just after the vessel entered the intestine. Better areas for the demonstration of the lesions seen during life are shown in case 3. In the sections submitted with the gross material typical lesions of periarteritis nodosa were noted with thrombosis, infarction and acute necrotizing panarteritis. Many healed lesions were present in the intestine and kidney with

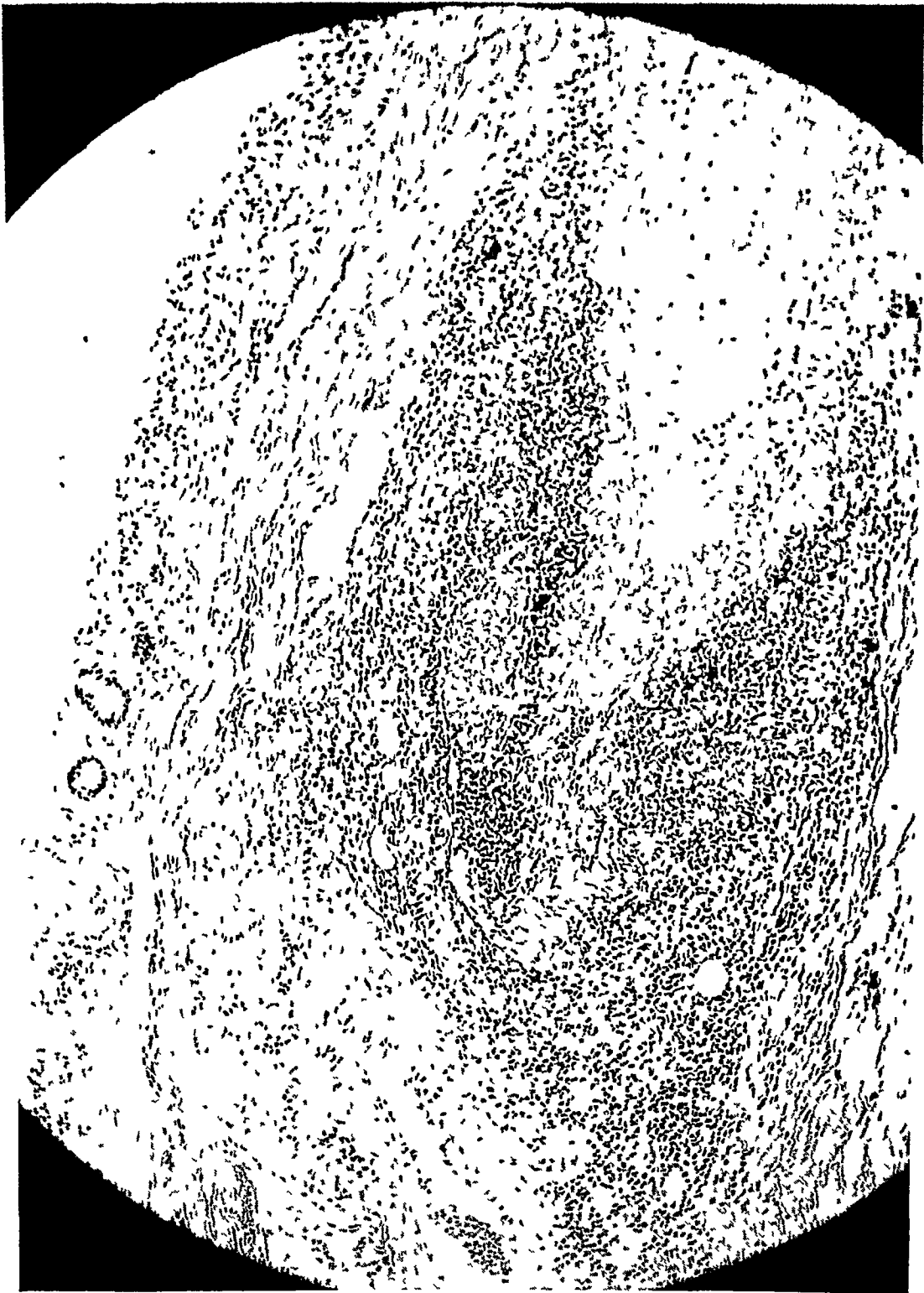


Fig 5 Acute necrotizing pancreatitis in a submucosal vessel which is thrombosed. Note intact mucosa.

recanalization and perivascular mantles of fibrosis and round cell infiltration. There was a recent massive hemorrhagic infarction of the myocardium. Various stages of the disease could be detected in different organs or even in different parts of the same section.

Case 2 L A, female, aged 59 years, was admitted to Fordham Hospital on April 15, 1935, with a history of having had pain and a feeling of "pins and needles" in both feet for six weeks. Her feet felt cold and some relief was obtained by means of rest and the application of heat. Movement of the feet was painful. There was no evidence of vascular occlusion. Roentgenographic examination of the chest and both feet was negative. The blood chemistry and urine examination were normal. The blood pressure was 160 mm systolic, 100 mm diastolic. The blood count revealed nothing distinctive and the patient was discharged on April 20 with a diagnosis of arteriosclerosis of the deep vessels in the lower extremity.

One year later (April 23, 1936) the patient entered The Bronx Hospital complaining of coldness and heaviness in the lower extremities for six weeks and vomiting for five days. She stated that at the time of her previous hospitalization a skin rash and fever had been prominent symptoms. For the past few days the patient was unable to walk and suffered an attack of diarrhea and abdominal cramps lasting 24 hours. Physical examination revealed an aged woman, not acutely ill. The blood pressure was 180 mm systolic, 104 mm diastolic. The heart was enlarged to the left. There was a complete paralysis of the peronei of the left leg. The skin of both lower extremities had a mottled purplish discoloration which faded on pressure. Pulsations were felt in the vessels of both legs, but their elevation to a 45° angle did not produce blanching until one minute and it was not complete for another two minutes. There was impaired sensation to touch and pain on the inner and lower aspects of both legs. Knee jerks were present, but the left ankle jerk was absent. Neurological examination revealed involvement of the peripheral sensory fibers of the anterior tibial nerve and left foot drop. An indefinite mass was felt in the epigastrium. On April 28 the Rumpel-Leeds test was positive at the end of 15 minutes. On April 29 a painful tender mass which appeared to be an enlarged spleen was noted in the left upper quadrant of the abdomen. Repeated vomiting and abdominal cramps were present. The possibility of an acute surgical abdomen was considered with intraperitoneal hemorrhage due to a small rent in the spleen. A diagnosis of thrombosis of the splenic vein was made and on April 29 laparotomy (Dr. Wells) revealed a grapefruit-sized retroperitoneal mass in the left upper abdomen. The general shape resembled that of the kidney. The temperature ranged between 99° and 101° F and pulse 80 to 120. The patient expired on April 30, twenty-four hours after operation.

The laboratory findings were as follows:

Blood counts

Date	Hgb	RBC	WBC	PN	SL	Bd	Other Forms
4-23	53%	3,300,000	26,100	86	11	0	3
4-27	56%	3,300,000	33,500	77	19	2	2
4-29	34%	2,000,000	35,000	73	10	9	8

No eosinophiles were seen.

On April 24 the reticulocytes were 0.2 per cent and platelets 240,000 per cu mm. On April 26 the sedimentation rate was 18 mm in 16 minutes. The Wassermann reaction was negative. The icteric index was 8.4, Van den Bergh direct delayed and indirect 0.7 units per 100 cc. Gastric analysis showed a free acid of 6.5 and total

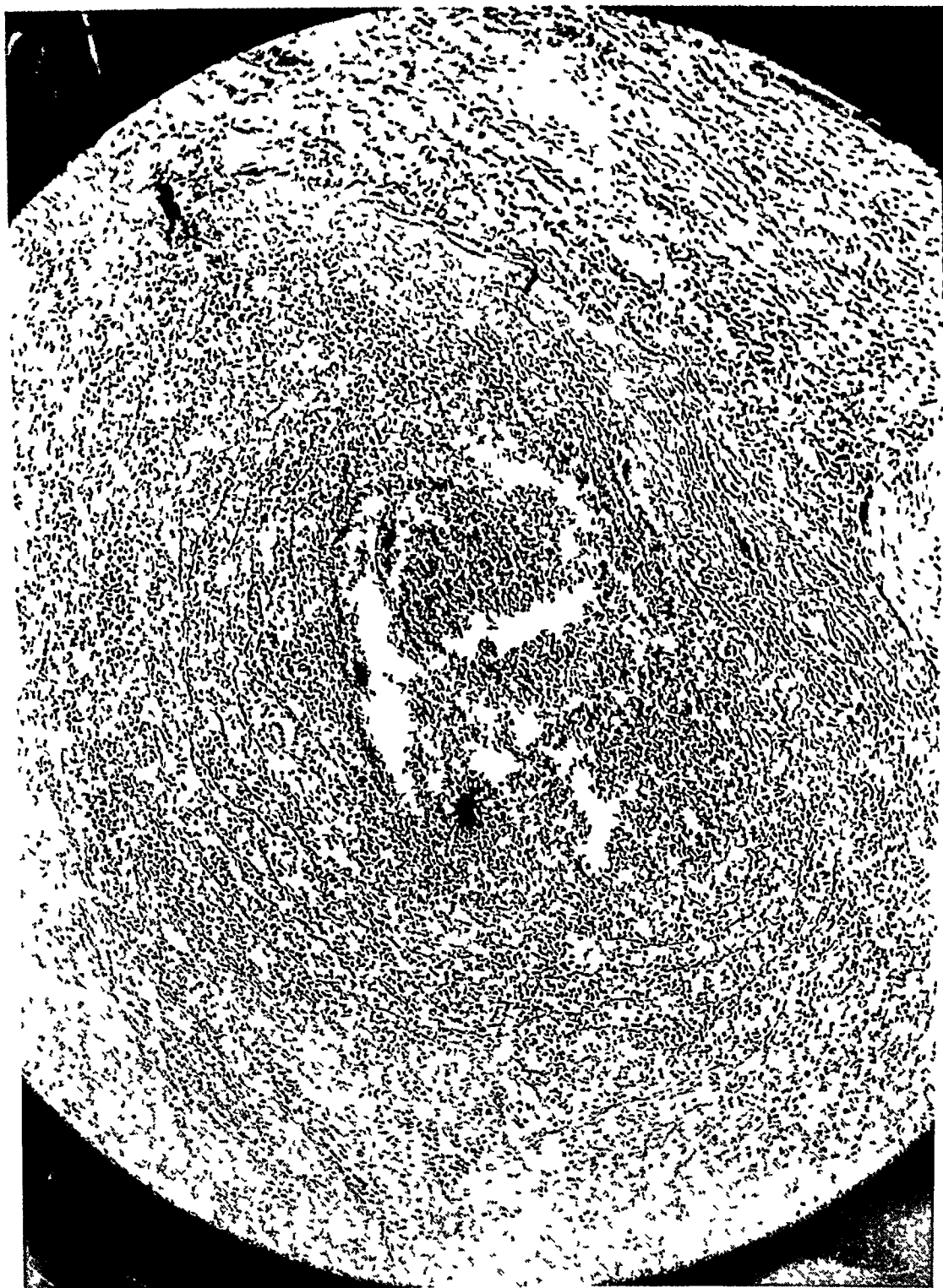


FIG 6 Acute exudative type of inflammation involving all coats of the artery with edema, cellular infiltration, necrosis and thrombosis



FIG 7 Partially healed vessel with perinodular fibrosis, organization of the thrombus by fibroblasts and beginning recanalization Note nodule at right and intact elastica at left

and of 25. On April 27 a Mosenthal test indicated a tendency to fixation of specific gravity between 1.014 and 1.016. The urine contained albumin and granular casts on one occasion. The blood urea, glucose, uric acid and creatinine were normal.

Cut section of the gross kidney specimen revealed the characteristic lesions of periarteritis nodosa with massive infarction of renal tissue. Small and large thrombosed vessels were clearly visible to the naked eye with perimodular or aneurysmal formation and hemorrhage. The histopathology revealed changes varying from medial and subintimal necrosis to complete disintegration of the wall with rupture and hemorrhage into the adjacent parenchyma. The vessel wall was thickened, edematous and the fibers separated by inflammatory cells chiefly of the polymorphonuclear neutrophilic, eosinophilic, lymphocytic and plasma cell varieties. In some fibrosis had already replaced the periarterial nodule and organization and recanalization of the thrombi were seen.

Case 3 Since the general aspects of this case have been reported by Sandler, only the intestinal material borrowed for study will be presented. The patient was a white male, aged 54 years, and the total duration of illness was approximately one year. The outstanding clinical features were multiple skin nodules, muscle spasms and weakness, abdominal pain and a left hemiparesis. The blood examinations revealed a secondary anemia, a leukocytosis of 21,000 with 55 per cent eosinophiles. About two months later the leukocytes fell to 14,000 and only an occasional eosinophile was noted. A clinical diagnosis of periarteritis nodosa was made (Dr. Sandler) and at necropsy characteristic vascular lesions were found in the heart, lung, liver, spleen, kidney, gall-bladder, testis and intestine (Dr. Ehrlich).

Upon examination of the intestine obtained at necropsy there were seen two types of gross lesion, viz. nodular and linear. When viewed as a transparency, the nodular lesions stood out as oval, localized, hemorrhagic protrusions of the vessel wall from which the delicate proximal mesenteric branch emerged rather abruptly. In some instances it appeared as though there was a tendency for the process to extend slightly beyond the confines of the nodular lesion along the course of the vessel. The linear lesions involved the vessel in a uniform and longitudinal fashion, standing out as rigid, dark red thrombosed cords which elevated the tissue above it. The intramural vascular lesions were clearly visible through the intestinal mucosa which was slightly raised. The general direction was transverse corresponding to the manner in which the vessels normally encircled the intestinal wall. A rather striking feature was the "skip" or segmental nature of the vascular lesions, linear or nodular thrombosed areas alternating with apparently normal portions of the vessel. Often this could be traced in the mesenteric and intramural branches of the same artery. Microscopic sections revealed an intact mucosa with acute necrotizing panarteritis of the small submucosal arteries. The close proximity of these branches to the mucosa accounted for their easy visualization in the gross specimen. Thrombosis, necrosis of the wall with partial destruction of elastica, periarterial nodule and aneurysmal formation with rupture and perivascular hemorrhage were the essential histopathological features. In some sections partial organization of the thrombus was taking place by young fibroblasts and there appeared to be some recanalization. Considerable vascular and perivascular infiltration by polymorphonuclear leukocytes and mononuclear cells was evident in vessels which were still intact.

DISCUSSION

Perusal of the data presented in these cases reveals the presence of the characteristic diagnostic tetrad of Meyer and Binkman in each instance, viz chlorotic matasmus, abdominal manifestations, nephritis and polyneuritis, polymyositis. In each of two cases (1 and 3) there was a high eosinophilia, a finding common to relatively few diseases, one of them being periarteritis nodosa. Its absence does not exclude the disease (e.g. case 2) since, according to Arkin,⁷ marked eosinophilia is encountered chiefly in stage 2 or 3 (acute inflammatory or granulation tissue stage), being negligible or absent in stages 1 and 4 (degenerative and healed stages respectively). In cases 1 and 3 the eosinophilia, present at the height of the acute phase, disappeared several months before death.

The essential pathological features of periarteritis nodosa consist of a necrotizing panarteritis affecting chiefly the vessels of the kidney, heart, gastrointestinal tract, mesentery, liver, muscles, cranial and peripheral nerves in approximate order of frequency. The noxious agent enters the vessel wall either directly from the lumen or through the vasa vasorum of larger vessels (Arkin). There is produced an exudative type of inflammation in the media with edema, fibrin deposition, coagulation necrosis, cloudy swelling and hyaline degeneration of the muscle fibers. Similar subintimal changes may occur in the smaller arteries with almost complete obliteration of the vessel lumen. There is a diffuse cellular infiltration of the entire wall by plasma cells, lymphocytes and polymorphonuclear cells chiefly of the eosinophilic type. Microscopic involvement of the wall is generally linear. The fibrinous and cellular exudate extends to the intima and adventitia, the elastica becomes fragmented and thrombosis occurs, in other instances necrosis of the media with subsequent weakening of the wall is followed by aneurysm-like formation and rupture into the surrounding tissue. The process as described comprises stages 1 and 2 or degenerative and acute inflammatory stages, respectively. These and the other two blend imperceptibly with one another or more than one stage may be present in different vessels simultaneously. The acute inflammatory stage is followed by a proliferative or granulation tissue stage (stage 3) in which fibroblasts and thin walled blood vessels grow into the damaged areas producing subendothelial thickening or even invading the thrombus within the lumen. Recanalization may occur or complete occlusion of the vessel. The same reparative process occurs in the media and adventitia, an area of proliferative fibrosis replacing these layers and often the zone of perivascular aneurysmal or nodular formation. Sometimes a linear mantle of periarterial fibrosis without nodule formation is seen, particularly where the lesions are linear in the first place (stage 4 or healed stage).

The etiologic agent of periarteritis nodosa has not been definitely established. In general, there are three schools of thought, viz (1) Specific virus (Arkin, Haining and Kimball), (2) rheumatic (Ophuls, v Glahn and

Pappenheimer, Friedberg and Gross), (3) post-infective mesenteritis (Spino, Gruber)

According to Arkin, clinical diagnosis is possible only in stages 2 and 3. Infarction, atrophy or scarring of the organs supplied by affected vessels may offer an indirect clue, but the real underlying pathology is generally not ascertained during life. Wever and Perry⁴ reported a case of fatal perirenal hemorrhage in which the condition was deemed surgical very much like case 2 with renal infarction reported above. Fever is present during the active stages (1 to 3) and absent in stage 4, according to Arkin. Focal lesions in various organs are common, but difficult to interpret even in the presence of a leukocytosis as seen in stage 2. Coronary or renal involvement is relatively frequent, but more common causes than periarteritis nodosa are generally suspected. Involvement of the extra- or intramural intestinal vessels appears to be much more frequent than retinal involvement and offers a promising field for non-operative clinical diagnosis since visualization of the intramural branches was actually effected in our patient. Arkin has even described a rather picturesque involvement of the mesenteric vessels (as seen at necropsy) in which hempseed-like nodules studded the vessels like a string of pearls (perlschnurartig). The intramural "skip" or segmental involvement which we noted at sigmoidoscopy is probably part of a similar picture. Intestinal symptoms and signs consist chiefly of cramps and diarrhea which appear to be due to involvement of the larger extramural branches with subsequent anoxemia of the part of the intestine supplied. Thrombosis of the principal mesenteric arteries with intestinal infarction is uncommon. Involvement of the smaller intramural branches alone is rarely extensive enough to produce anoxemia as their rich arborizations are sufficient to maintain an adequate blood supply. No broad assumptions can be made on the basis of our limited experience, but in view of the fact that intestinal lesions are so common in periarteritis nodosa, their detection at sigmoidoscopy may prove to be a useful diagnostic procedure in this disease.

SUMMARY

Correlated clinical and pathological studies have been presented in a case of periarteritis nodosa diagnosed during life by sigmoidoscopy.

REFERENCES

- 1 MIDDLETON, W. S., and McCARTER, J. C. The diagnosis of periarteritis nodosa, *Am. Jr. Med. Sci.*, 1935, cxc, 291.
- 2 SANDLER, B. P. Periarteritis nodosa. Report of a case diagnosed clinically and confirmed by necropsy, *Am. Jr. Med. Sci.*, 1938, cxcv, 651.
- 3 ARKIN, A. A clinical and pathological study of periarteritis nodosa, *Am. Jr. Path.*, 1930, xxxiv, 401.
- 4 WEVER, G. K., and PERRY, I. H. Periarteritis nodosa. Report of a case with fatal perirenal hemorrhage, *Jr. Am. Med. Assoc.*, 1935, civ, 1390.

SOME PROBLEMS CONFRONTING THE PHYSICIAN IN THE EXAMINATION OF AUTO- MOBILE DRIVERS [†]

By LOWELL S SELLING, M D , P H D , D R P H , F A C P ,
Detroit, Michigan

THE history of medicine has demonstrated over and over again the alertness of the physician to meet new problems. When firearms were introduced into the art of warfare surgeons rapidly learned new technics of saving life. With an increased use of machinery in industry, industrial medicine and surgery have shown a parallel development. But strangely enough, in dealing with the medical aspects of the traffic problem, there is a detectable lag.

The real problems set up by the existence of the motor car have not been apparent until the last 15 years. Surgery has met the particular emergency set up by the motor car because of the fact that surgical technic can be adapted to various purposes and because injury due to violence in its essentials is very much the same whether caused by a motor car or by an axe or a club. The problem of medicine in the consideration of the damage done by motor cars is somewhat different. The medical man is asked to take part in the solution of this problem from two angles.

The first is the problem of what part the physical or mental condition of the patient may have played in causing the accident and in determining the patient's responsibility for it, and what important medical changes have occurred to the patient or others as the result of an accident. This last consideration, I think, is more important in a civil case than in a criminal one. It is sufficient, in the criminal court, to show that damage was done to the victim, the amount of damage must be assessed in the civil court.

The second problem, and the greater one, is to determine who should drive. Here the fields of preventive medicine, general medicine, and law overlap. The matter is important from the standpoint of preventive medicine because public health demands that the mortality and morbidity due to automobile accidents be curbed. When we consider that two years ago 40,000 people were killed in the United States from this cause alone, the problem cannot be ignored. Even last year (1939), which was considered a fair year, there were still about 32,000 people killed and 1,200,000 injured throughout the country [†]. It is not the public health worker, however, who

* Received for publication July 18, 1940

(Presented in part at a meeting of the Noon Day Study Club of the Wayne County Medical Society, Detroit, Michigan, April 4, 1939, under the title of "The Function of the Physician in the Examination of Drivers")

From the Psychopathic Clinic of the Recorder's Court, Traffic Division, Detroit, Michigan. Series T, No 17

[†] From "Smash Hits of the Year, The Travelers 1940 Book of Street and Highway Accident Data, Hartford, Connecticut, The Travelers Insurance Company, 1940, page 3

can make the examination or do the research to determine what constitutes a satisfactory physical condition in one who wishes to operate a motor car.

One aspect of this problem lies in the question of whether the criteria and standards set up by various consultants, including physicians at the request of license bureaus and other law enforcement agencies, can be sustained in a court of law. It is easy enough to set up hypothetical standards, but it remains a matter deserving of considerable thought to determine whether there is definite evidence of the validity of these standards which can be laid before the judge in an honest and convincing manner.

The problem of medical standards for safe drivers is one in which few medical men can qualify as real experts inasmuch as very little research has been done outside of that which we have done in the Psychopathic Clinic of the Recorder's Court in Detroit.^{1, 2} When the Clinic was set up in October of 1936, as a joint project sponsored by the Judges of the Traffic Division of the Recorder's Court and the Judges of the Recorder's Court, the personnel of the Clinic canvassed the literature to see what definite information there might be on the subject of personal driving standards. A resolution presented by the Section on Ophthalmology, coordinated with one from the Committee on Physical Standards for Drivers of Motor Vehicles, was adopted by the House of Delegates of the American Medical Association, setting forth quite reasonable standards.³ New standards were set up in 1938 but they are still open to severe criticism.⁴ In spite of the fact that certain rather gross examination standards have been set up in the driving laws of some states, the physician remains at loose ends. Most medico-legal terms have not been adequately defined as regards psychiatry and, perhaps, as regards medicine in general, but the standards, grossly, are that, in various states, the following are disqualified: habitual drunkards or drug addicts (25 states), insane or feeble-minded (18 states), idiots, imbeciles or epileptics (17 states), persons having physical or mental defects causing lack of reasonable driving control (22 states), persons adjudged afflicted with a mental disability or disease (7 states). There are also states where the deprivation of license is mandatory when certain of the above conditions are present.⁵

However, from the point of view of utilizing these laws so that they will be most valuable to the driving public much remains in question. For example: Shall imbecility be determined by a clinical definition or by virtue of a dead-level intelligence quotient? Do enough persons afflicted with petit mal know that they are suffering from epilepsy so that they can be made to report under these laws? Does hystero-epilepsy, a functional disease, fall under the gross head of epilepsy in dealing with traffic problems?

These and many other questions arise in the administration of the medical problems of traffic. Standards for these are, therefore, in a confused state. Visual defect standards are based on those urged by the National Safety Council and defined by the Ophthalmology Section of the American Medical Association. Those of crippling are merely whatever the examiner and the

Police Department wish to call severe crippling as determined by the way the man can operate a motor car on a road test. In the Clinic we have seen many sufferers from infantile paralysis, all of whom could operate a motor car well enough to pass a driving test, but who in a sudden emergency were unable to react quickly enough to bring their withered limb into action with sufficient strength to keep from having an accident. There is no question but that with special apparatus and in certain special cases the sufferer from infantile paralysis is a safe driver, as determined by a road test, but the standards themselves remain to be established. Perhaps all-inclusive standards will be too difficult to develop and each case will need to be evaluated on its merits.

The first consideration for the physician is his obligation to give competent advice to the Court in determining how culpable an individual involved in a traffic accident might have been.⁶ There have been a number of persons brought into the Recorder's Court Traffic and Ordinance Division who have maintained that they were ill and, therefore, not responsible for the accident in which they were involved. As a general rule, the Judges of the Recorder's Court Traffic Division have referred such cases to the Clinic for an evaluation. This is not because they doubted the reliability of the physician who had given a certificate which stated that the man was not in good physical condition, but because it does, in their opinion, require a special ability to evaluate how important these physical disabilities were in the specific situation. The testimony of the physician in Court regarding a man's condition, and its evaluation in the sense of indicating responsibility or lack of responsibility for an accident, requires a knowledge of the special capacities needed for operating a motor car. There is, however, no difference in the need for special training between the physician who is willing to give a certificate to enable a patient to escape the consequences of his act and the physician who is able to make special examinations for the purpose of recommending whether a man should or should not have a license.

In general, then, there are three considerations which cannot be overlooked in evaluating a person's physical condition to decide whether he was responsible at the time of committing an offense or having an accident, or whether he is physically able to drive a car. There are a number of traditions and facts on the subject, but in general we might say that these three conditions are: first, an adequate mentality, second, an adequate physical condition, including, of course, an intact central nervous system, and, third, adequate vision, which is tied up, of course, with both the first and second considerations.²

For the time being I shall mention the psychiatric side only very briefly. It is sufficient for the physician to know that the psychiatric side cannot be ignored. Many a man whose physical condition is such that one would consider him unfit to drive might very well be permitted to drive because of his intelligence, his favorable attitude, his knowledge of his weaknesses, and a

desire to compensate, which he can do by not driving on slippery days and nights or in heavy traffic.

The Clinic has seen many color-blind individuals who have proved to be so by the test, but who were not to their own knowledge actually color-blind. They had never had any difficulty in distinguishing between the red and the green lights, and until we pointed out to them that on the Ishihara test they were unable to distinguish between red and green letters and numerals, the fact that they were color-blind was entirely unknown to them. Most of these cases (and we found about 4 per cent of our cases to be partially or completely color-blind) are able to drive cars and to keep out of trouble. They were not referred to the Clinic because of their color-blindness. They were usually referred because of some other weakness that had been brought to the attention of the Court. All but three of these cases were able to tell the difference between the red and green lights and this was not due to the position of the lights on the standards, because in our Clinic we move these lenses around. The worst color-blind cases were two seriously feeble-minded individuals who had got into a great deal of trouble. Their offenses had not been numerous, but were quite serious. In one case the man had actually gone through a red light against traffic, seemed to be quite bewildered by the fact that traffic was going in the opposite direction, and was unable to compensate for his color-blindness because of his feeble-mindedness.

In evaluating the importance of physical ailments in the driver, his mental condition must not be ignored. If the physician is examining a man because he wants to get out of the consequences of his violation, or because he has been refused a license and wants his physician to speak to the License Appeal Board in his behalf, the physician would do well to note a few important psychiatric considerations.^{7, 8} The first one is: What is the patient's attitude? Does he have a feeling that the driving privilege is one which is given to him by the Constitution or by God, and that nobody has the right to take it away from him? If he explains any accidents or difficulties in which he has been involved, does he always take the attitude that it is the other man's fault, that he could not possibly have been at fault? If this is the case, it would pay one to be very suspicious. It is undoubtedly true that many people have accidents for which they are not to blame, but it has been my experience, after seeing almost 800 cases of this sort, that even the allegedly innocent party contributes in some measure to an accident.

The attitude taken by most modern traffic courts in this connection is that if a man is not able to stop in time, even if he has the right-of-way, he is almost as much at fault as the offender who drove across the right-of-way, making it necessary for the victim to stop. The good driver, the one who is not violating the traffic laws, is able to stop in time to avoid an accident. However, it must be admitted that there are situations which arise where the conditions are so misleading (such as a blind corner or other trap which is improperly marked) that although the man may be taking due care, he does get into trouble. In these days, in view of the thousands of dollars

being spent on markers, signs, and other indicators to prevent an individual's going too fast in a dangerous place, it is rather a doubtful excuse for the defendant to say that the emergency arose so quickly that he could not react in time.

If an individual, who is to appear before a License Appeal Board or similar examining body for a hearing to determine whether he should have a license, wishes to bring with him a doctor's certificate, it would be well for the doctor who examines him to make an investigation as to any signs and symptoms of psychosis. There are very definitely a number of insane individuals driving who show a suggestion of a paranoid picture or in whom the neurological examination indicates faint signs of central nervous system syphilis, and the doctor may be jeopardizing his reputation by giving a man of this sort a certificate so that he will be granted a driver's license.

To evaluate the general physical condition of the driver does not require any unusual technic. Any competent physician can recognize signs of arteriosclerosis, nephritis, systemic disease, and metabolic disease in these days. Even rather early cases are detectable clinically, although occasionally it is true that the laboratory must be brought in to assist. Just how sick a man must be before he should not drive is a problem which has not yet been adequately studied. I do not know of any really good standards. In certain foreign countries the rule is that if there is any degree of illness at all, the man should not be permitted to drive.⁹ If such a broad ruling is invoked, the diabetics, the mild arteriosclerotics, the mild sufferers from poliomyelitis, and the mild nephritics are handicapped and are unable to go about their business when quite possibly they are safe drivers.

A number of reporters in Europe admit that the too strict attitude should be revised, and it is becoming the duty of clinics such as ours in Detroit to establish new standards. We will require the help of the medical profession in doing this. Sooner or later we will have to circularize physicians and find out from them which cases have had accidents and which have not. But the time does not appear to be ripe.

Nevertheless, I shall present a few experiences, and some opinions about physical disorders which we feel to be justified. We have had a large number of arteriosclerotics coming through our Clinic. We have had 15 cases where the blood pressure was over 160, in half of these cases there had been an accident. In none of them was the accident serious nor was there a death, so that we might say that the mere presence of high blood pressure should not make it necessary to take away a man's driving privileges. However, if there is any danger of syncope—and this must probably be left for decision to the doctor's own experience—a man suffering from hypertension of any sort might well be advised not to drive. If he has never had a syncopal attack, if his blood pressure seldom goes over 180, careful observation of his conduct and evaluation of his subjective syndromes might make it possible to state that he was competent to drive. I would be skeptical about serious cases, but I would not like to lay down any hard and fast rule.

We have seen a few diabetics. Most of them did not come to our attention because of their symptoms, for usually they had already been placed under treatment. In one case, that of a feeble-minded Negro who was taking insulin, the man decided after taking his noon-day injection that he would go for a drive before he had his lunch. The subsequent accident, which resulted in injury to nobody but which badly battered several cars, was probably due more to his feeble-mindedness than to the condition of his blood sugar. I have checked with several physicians who have large diabetic practices, and it is their opinion that diabetes per se, particularly the milder or well controlled forms, is not a contra-indication to driving. However, it is well for a patient who is taking insulin to be warned that he must not drive his car until he has eaten an adequate meal after the injection. Of course, any intelligent diabetic will carry with him a supply of readily available carbohydrates. We have been promised by the Detroit Diabetic Association that it will make a survey for us to determine whether there is any accident tendency among the patients under their observation. I very much doubt whether such a tendency exists.

Cardiacs are very serious problems because we have in the accident reports a number of casualties where a man known to have heart attacks has lost consciousness or has died suddenly at the wheel. Any man with severe syphilitic aortitis or an active endocarditis certainly should not drive. The arteriosclerotic heart, many instances of which have been seen in the Clinic, does not seem to have interfered with the patient's driving ability, particularly in its milder forms. Nevertheless, if the patient has had a history of decompensation, he should be warned that he must not drive if he has any dyspnea or other signs of beginning decompensation, and if he is to keep his license, he should be checked rather frequently by his physician. He need not necessarily be deprived of his license, but it should be limited. Some day perhaps we will have to have endorsements on these licenses to indicate that the periodic examination is being carried out. The expense and hardship of such periodic examinations probably would be much less than the expense and hardships the man would have to undergo were he unnecessarily to be deprived of his driving privilege. By the time a man has severe arteriosclerotic heart disease it is quite possible that he will have other weaknesses, particularly in reaction time, in the nervous system, or in vision, which would make him a risk on the highway.

These are the chief systemic diseases which have been brought to our attention. We are making a special study of neurological disorders, particularly of sufferers from infantile paralysis of whom there are many, and it has been the opinion of the local licensing authorities that if such cases can operate a car to the satisfaction of the examiners of the State Police, they should be permitted to drive. We have had some of them referred to the Clinic because of minor accidents, and the cases have had to be evaluated on the type and degree of disability. For instance, the last case we saw, a young man 18 years of age who had only had about three weeks' driving

experience, had completely paralyzed lower extremities on both sides and a partially paralyzed right arm. Now, this man could not adequately handle the pedals of his car even though he kept his feet upon them and pushed his knees down manually to depress them. Because of this, he ran into the back of a truck, did not do much harm, but revealed to us and to the Court that he was a greater risk on the highway than the normal individual, and that the chances were high that he would never be a safe driver. We always feel very sorry for these individuals, and a good deal of pressure has been brought to bear upon us to be lenient with them for economic reasons. We can never see why an individual's economic life should be held superior to the life of a victim.

There is no question that the eye findings in the case of license candidates, or in one who is trying to escape the consequences of his traffic misdeed, are important, but just what should be considered significant and what the standards should be, I do not think have properly been determined as yet. I mentioned above the fact that color-blindness, which is supposed to be very important in traffic, has been, in our experience, of rather small significance. Color-blindness and limited fields of vision are stressed by some psychologists and by amateurs in the field of physical and mental examinations of traffic offenders, but, out of 760 cases, we found only eight with marked diminution of the field and these were obviously suffering from diffuse neurological diseases, and their inability to drive was so obvious that they were never granted licenses.

Paretics, of course, have limited fields of vision, but their symptoms can be detected through the usual neuropsychiatric examination.

Visual acuity standards have been set up by the Section on Ophthalmology of the American Medical Association, but these standards have, in my experiences, worked some injustices because of over-strict application by lay eye-testers. In many cases the competent ophthalmologist can set aside these standards without permitting a dangerous driver to be at large on the highway^{10, 11}

The Clinic has seen several cases where the vision in both eyes has been as low as 20/200, yet the individuals have never been in any trouble. One of them, referred for research purposes, was a truck driver with over 500,000 miles of driving experience, who was found to have a very low visual acuity. Nevertheless, his route was distinctly channelized, he followed the same streets day in and day out, he drove rather slowly, was very alert, very cautious, and very anxious to maintain a good record, his poor vision was not a handicap, and we do not expect to find him in the Clinic unless he deteriorates.

There are a number of other functions of vision which are partly psychological, such as depth perception, judgment of speed and distances, and judgment of spatial relationships^{12, 13}. These all require special apparatus for their proper testing, and the average physician would not find it worthwhile to have this equipment. If the physician is doubtful about a man's vision,

it would be well for him to call in a consultant or, if it is possible, as in Detroit, to refer the man to a Clinic, such as ours, so that he might be given a certain amount of specialized advice about his patient's eye condition.¹⁴

The help of the physician has been asked in numerous cases involving intoxication while operating a motor vehicle. Physicians are sometimes asked to testify in Court that the individual facing a charge of drunken driving was really sick at the time of his accident or arrest and that alcohol was only secondary. Occasionally the physician is asked to state under oath that the patient was not drinking at all and that the appearance of alcoholism was the result of the use of drugs, of family trouble which resulted in "nervousness," of fatigue, or of some other cause. The experience of the Clinic leads one to believe that upon occasion the ends of justice are decidedly served by the testimony of the medical expert in such cases. Certainly, for instance, a man should not be sentenced for drunken driving if he had not been drinking but had suffered a cardiac attack which caused him to stagger and faint. Nevertheless, the physician who testifies in such cases has not done his whole duty, particularly if he is the family doctor, if he does not follow up the circumstances surrounding the traffic violation or accident. If the patient is subject to convulsive attacks, his physician should warn him not to drive. It would certainly not be unethical for a physician to urge the man to surrender his license.

The greatest circumspection should be used in testifying in cases involving drunkenness. Physicians have been made dupes by casual acquaintances, and by patients who have been drinking and whose drinking, while it might perhaps not have been the critical factor, was definitely a contributing factor in the accident. Physicians must not forget that even small doses of alcohol administered to certain physically and mentally weak cases will make them dangerous on the highway, whereas they might not be from their physical ailments alone. Syphilis is an example of such a situation. We have on record the case of a sufferer from syphilis evidencing very mild central nervous system manifestations who normally was qualified to operate a car but who, after having only a little beer, was subject to convulsions.

Although the Committee to Study Problems of Motor Vehicle Accidents of the American Medical Association has set up standards for the amount of alcohol in the blood which constitutes drunkenness, the value of these standards is open to question.¹⁵ The amount of alcohol concentration resulting in drunkenness is now set at 15 per cent by weight. This is probably too high to include the majority of dangerously drunken drivers. Certainly an individual who has that much alcohol in his blood is not a good risk on the highway and should be sentenced as a drunken driver, but the majority of individuals who absorb that much alcohol are really incapable of sitting behind the wheel of a motor vehicle and operating it, and consequently "pass out" before they try driving. We seldom see individuals as intoxicated as this arrested for drunken driving, in fact, a truthful history of "a few beers" taken on an empty stomach is the usual one.

The physician who knows a chronic alcoholic of this sort would do well to prevent his driving a car, for the probabilities are that, if he gets into trouble even though it is due to no fault of his own, he will be sentenced as a drunken driver and, in most states and cities, especially in Detroit, he will be given the most severe penalty the judges can devise

It is not to be expected that the physician in private practice will have apparatus for testing the breath, urine or blood, and it is open to serious doubt among lawyers whether such tests might violate the patient's constitutional rights if he were compelled to submit to them. Since in many cases the tests are administered by a layman (police officer), their validity will for a long time be open to question. If such tests are to be given, it would be well for physicians to acquaint themselves with the intricacies of their chemistry so as to qualify as experts in this respect when called upon to testify in drunken driving cases

In conclusion, I should like to cite a case. A 63 year old man was sent to the Clinic by one of our traffic judges. His blood pressure was only 140 mm mercury systolic and 80 mm diastolic, but his vessels were tortuous, and we could feel in the arms definite indication of thickening of the walls, almost to the degree of a pipestem vessel. His judgment of speed and distance, his reaction time, and his depth perception were poor. On the intelligence test he rated only an intelligence quotient of 70, which was about that of a nine-year-old child. This might not be bad in a younger man, but was probably an indication of deterioration in his case because in the past he had been a rather good salesman. He was over-talkative, silly, and showed signs of beginning arteriosclerotic psychosis. We examined him thoroughly, gave him all sorts of physical examinations, urinalysis, serology, tested his eyes by every possible means, and came to the conclusion that he was not a safe driver on the highway. We might note, too, that he had received over 150 tickets for minor traffic offenses. He had settled these with impunity at the Violations Bureau. When he was brought before the Judge, he talked in such a foolish fashion that the Judge sent him to us. He told the Judge that he had committed his last violation in order to come up and talk to him. After we recommended the revocation of this man's license, our recommendation was followed up by the Judge and the Secretary of State's office. The man immediately set in motion the procedure to get his driver's license back. Merely on his record we would have thought that his application would have been rejected, but our report was requested and transmitted to the Appeal Board, and on the basis of it he was turned down. When he was rejected this time, he went to a local neuropsychiatrist, and told him that he had been unfairly treated at the Clinic. This physician examined him, gave him a neurological examination but without doing any psychiatric inventory, did not notice the tortuous vessels apparently and, of course, not having the special apparatus for testing his eyesight, thought that even though the visual acuity was inferior, the man had adequate vision. The doctor wrote a letter to this effect to the Appeal Board which still withheld the man's license. The

patient's lawyer then said that he would take the case to the Circuit Court (the tribunal hearing such appeals), if the man would pay enough money. The petitioner tried to get the doctor's certificate for the lawyer, but in the interim the physician had communicated with us and been informed of our findings, so that he realized that the man had made improper use of his services, and, therefore, refused to issue another certificate. The petitioner then secured another lawyer who took the case to the Circuit Court and subpoenaed one of the best surgeons in town to testify concerning the petitioner's ability to drive a car. This surgeon testified on the stand that he found no arteriosclerosis, and that the man's eyesight was good, but when asked what the man's mental condition was, he said he was not a psychiatrist, probably because he realized from the petitioner's conduct when he was on the stand that there must be something the matter with his patient's mentality. Both of these doctors would have been well forewarned had they talked the matter over with us in the Clinic, or had they made a special study of the traffic situation with special reference to its medical aspects.

Naturally, the Clinic has no axe to grind. It is impartial, having a desire only to protect the driver from his own folly, and to protect the public from a dangerous driver. Often cases who are handicapped and who would make a poor impression before a Jury are warned that although legally they can have a license, if they get into an accident the Jury would consider it to be their fault. As a general rule, it has been our experience that the doctor is foolish who advises a traffic court that a man is in poor physical condition and, therefore, is not responsible for his accident. This almost immediately means revocation of the license, unless the doctor has looked into the situation so thoroughly as to be able to prove that the occurrence was one which would not repeat itself during his patient's driving career. Of course, if the doctor is sure that the accident is an isolated incident, and that the syncope or other cause of an accident will not recur, he should not hesitate to state this to the Court (his patient is certainly entitled to such service), but the physician would do well to lean backward before sending such a patient back on the highway.

To conclude, then, it must be obvious that there is a very definite place for the physician in dealing with this traffic problem to aid cases to get justice either in the Courts or when trying to get a license, but very special considerations should enter the physician's mind before he puts himself on record in regard to the patient's condition in relation to his ability to drive a motor car.

REFERENCES

- 1 SELLING, L. S. The work of the psychopathic clinic of the Recorder's Court, University of Michigan Official Publication, 1938, xl, 31, 206-214
- 2 SELLING, L. S. The physician and the traffic problem, Jr Am Med Assoc, 1937, cviii, 2, 93-95
- 3 Resolution from the Section on Ophthalmology, Jr Am Med Assoc, 1925, lxxiv, 1743

- 4 Committee on Standards of the Ophthalmology Section of the American Medical Association Visual standards of motor vehicle operators, Jr Am Med Assoc, 1938, cxi, 716
- 5 Control of Automobile Drivers' Privileges in the United States, Legislative Bureau, Chicago Motor Club, Chicago, 1938, pages 4-7, 15-31
- 6 SELLING, L S Is the hit-skipper really a coward? Public Safety, 1938, xiv, 6, 14-15
- 7 SELLING, L S Personality traits observed in automobile drivers, Proc XI^e Congr Internat d Psychol, 1937, Paris *Also* Jr Criminal Psychopath, 1940, i, 256-263
- 8 SELLING, L S Mental pathology found in automobile drivers, Jr Criminal Psychopath 1940, i, 254-257
- 9 SIMONIN, CAMILLE L'Automobile homicide, Librario J B Bailliere et Fils, Paris, 1931
- 10 Visual standards for licensure to operate motor vehicles—a preliminary report of the Special Committee, read before the Section on Ophthalmology, Jr Am Med Assoc, 1937, civ, 61-B
- 11 Visual standards for operating motor vehicles, Jr Am Med Assoc, 1938, cxi, 716
- 12 SELLING, L S The psychological approach to the traffic problem, The Scientific Monthly, 1937, xlv, 547-554
- 13 SELLING, L S, and CANTY, ALAN Apparatus for psychophysical testing of automobile drivers, Jr Michigan State Med Soc, 1937, xxxvi, 283-284
- 14 SELLING, L S Abnormalities of the eye and their significance in traffic court cases, Jr Am Med Assoc, 1939, cxiii, 994-997
- 15 Committee to study problems of motor vehicle accidents, Jr Am Med Assoc, 1939, cxii 2164

CLINICAL STUDIES WITH THE AID OF RADIO-PHOSPHORUS. III. THE ABSORPTION AND DISTRIBUTION OF RADIO-PHOSPHORUS IN THE BLOOD OF, ITS EXCRETION BY, AND ITS THERAPEUTIC EFFECT ON, PATIENTS WITH POLYCYTHEMIA

By L A ERI, M D ,† and J H LAWRENCE, M D , *California*

THE purpose of this paper is (a) to indicate the amount of radio-phosphorus (P^{32}) retained by various fractions of blood of four normal individuals and six patients with polycythemia, (b) to indicate the amount of P^{32} excreted in the urine and feces of the normal individuals and some of the patients, and (c) to present the hematological and clinical findings of the patients before and after the administration of P^{32} ¹

MATERIALS AND METHODS

The radioactive phosphorus was produced by the Berkeley Cyclotron ² The four normal individuals were robust, ambulatory workmen with recently healed fractures, all of whom had received the same type and quantity of food for a period of from one to eight weeks, and each of whom had a single regular bowel movement daily during the same period, previous to the administration of P^{32} It was impossible to control the diets or time of excretion of the patients The blood withdrawn from veins was heparinized, cooled and centrifuged exactly 20 minutes at 1450 times gravity to insure constant volume The buffy coat was aspirated, suspended in equal amounts of heparinized Ringer's solution and centrifuged exactly 20 minutes at 1450 times gravity The plasma was then removed from the original tube and finally the red blood cells The stroma of the red blood cells and the phospholipid, acid soluble and nucleoprotein fractions of red and white blood cells and plasma were obtained by technics previously described ^{3, 4, 5, 6} The various blood samples and excreta of the patients and normal individuals were ashed at 400° C in appropriate crucibles, and assayed for radioactivity by use of an electrometer All the determinations of P^{32} recorded in the tables and graphs were corrected for decay to the date of administration ‡ One microcurie (μc) or 1/1000 millicurie (Mc) is equal to 37,000 beta particles per second

* Received for publication April 15, 1941

From the Radiation Laboratory and the Department of Medicine, University of California

This work was aided by the John and Mary R Markle Foundation

† Wm R Kenan, Jr, Fellow

‡ The half-life of P^{32} is 14.3 days

Results In table 1 are listed the four normal individuals and the six patients with their complaints and physical and laboratory findings before the initial administration of radio-phosphorus and the hematological changes and clinical results 7 to 15 months after the initial administration. In general the hemoglobin, red blood cell and white blood cell levels of the patients eventually reached near normal levels after various amounts of radio-phosphorus. There was marked clinical improvement and marked improvement in the physical findings in all of the patients during the period in which they were studied.

The average percentage of the dose of administered P^{32} retained per 100 c.c. of red blood cells, white blood cells and plasma of the normal individuals and of the patients are listed in table 2 and the red blood cell and

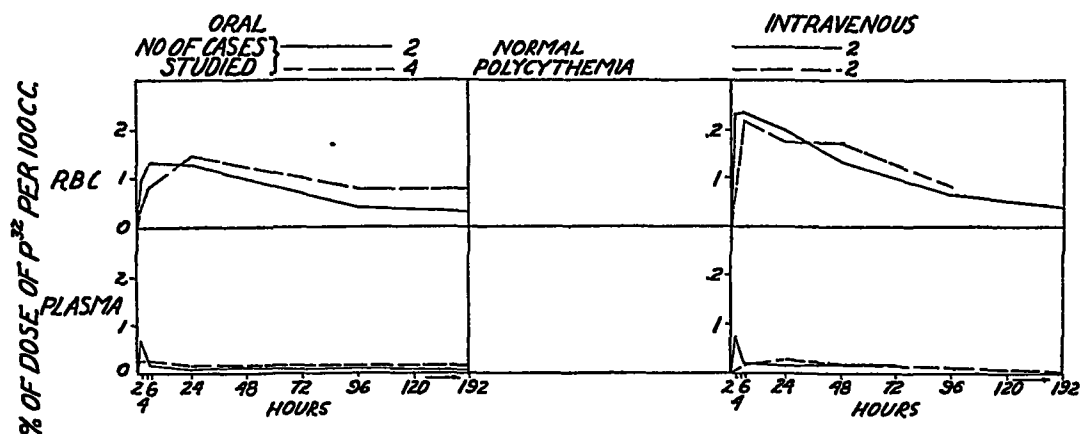


FIG 1 Average retention of P^{32} administered orally and intravenously in red blood cells and plasma of normal individuals and patients with polycythemia

plasma levels are illustrated in figure 1. The amounts and routes of administration of P^{32} , the number of cases studied and the intervals in time are noted also. No attempts were made to correct the findings for variations in the metabolic rate, blood volume, kidney and hepatic function, diet, age, weight, etc., of the cases studied. As can be observed in figure 1 the retention of radio-phosphorus in the red blood cells and plasma of both normal individuals and patients were nearly identical regardless of the route of administration. However, the retention of P^{32} in the red blood cells of both groups was higher following its administration by the intravenous route than by the oral route.

Table 3 presents the retention of P^{32} in various fractionations of red and white blood cells and plasma of two patients, one of whom (case 9) received the same number of millicuries of P^{32} on two occasions, once orally and once intravenously.

(a) Red blood cells. The levels of retention of P^{32} in the phospholipid fraction of the red blood cells of both patients increased during the 96-hour

TABLE I

Name, Number, Sex and Age	Date of Admission, 1940 (Nos 7 and 8, 1939)	Chief Complaints and Their Duration	Treatment before Admission	Physical Findings on Admission	Laboratory Findings on Admission					Treatment		Months after Initial Administration of Radio-phosphorus	Hematological Findings after Administration of P ₃₂				Results as of April 1, 1941	
					HB (%)	RBC (Thous)	WBC (Thous)	Platelets (Thous)	Retics (%)	M = Marrow (Sternal Puncture) H = Hyperplastic Blood Volume	Dates		Amount (Mcp) P ₃₂ Administered 0 = Oral 1 = Intravenously	HB (%)	RBC (Thous)	WBC (Thous)		Platelets (Thous)
1, 2	3	4	5	6						7	8	9	10		11			
1 Mie M-43	5-27	Fracture—external malleolus	None	Normal male	77.4350	6					7-22-40	1.5 (o)			No changes in blood levels during or follow- ing administration of P ₃₂ were noted in cases 1-4 inclusive			
2 Per M-35	7-19	Fracture—external malleolus	None	Normal male	85.4900	8					7-22-40	1.5 (1 v)						
3 Rob M-31	3-25	Fracture—radius	None	Normal male	93.5100	7					7-22-40	1.5 (1 v)						
4 Vic M-32	6-17	Wire removed from fracture	None	Normal male	85.4840	6					7-22-40	1.5 (1 v)						
5 Hay M-59	2-14	1 Headache 2 Plethora 3 Weakness 4 Mass and pain in upper left quad 5 Loss of wt	X-radiation at irregular intervals for 1 yr preceding admission	1 Plethoric 2 Spleen fills entire left abdomen 3 Liver—2 cm below costal margin 4 Hands very red	110.6600	55 Leuke- moid reaction	340			M—H (differential findings within normal limits)	2-16-40 2-26-40 3-21-40 8-10-40	3.96 8.16 7.00 8.00	3 6 9 12	86.1380 100.7590 106.6240 115	13,230 18 14 26	2,300 1,525 1,120 523	1.2 1.8 1.5 5	Symptomatic anemia for 9 mo preceding below left cervical mass—3 mo. Right cervical mass but no P ₃₂ administration since August 1940
6 Knu M-36	4-26	1 Headache 2 Weakness 3 Partial blindness 4 Hemiplegia (1939)	Numerous phlebotomies for a period of 1 yr preceding admission	1 Plethoric 2 Retinal hemorrhages 3 Hands red 4 Spastic paralysis —left extremities 5 Bedridden	121.6900	40 Leuke- moid reaction	600	1.4		M—H (shift to right in differential findings)	5-16-40 7-18-40 8-16-40 11-22-40 1-3-41 2-11-41 3-4-41	6.27 8.00 7.50 7.50 10.00 1.63 1.90	3 6 9 12	120.6920 119.6150 110.6590 101.5560	27,440 15,283 9,120 5,223	1.2 1.8 1.5 5	Symptomatic clinical and hematological improvement—9 mo Patient has been ambulatory for 9 mo	
												19.92						

Normal

7. Ian F-57	11-13	1 Dizziness 2 Headache 3 Plethora 4 Weakness 5 Staggering 6 Pain upper left quad.	2 yrs	Phlebotoxies every 2 wks for 1 yr preceding admission	1 Plethoric 2 Spleen—tender (2 cm below costal margin) 3 Hands red	120 7000	17	900 1 4	M—H (differential findings within normal limits)	11-24-39 12-12-39	5 34 7 00 } (o) 12 34	3 6 0 12 15	01 4080 8 280 07 4105 9 330 07 4600 13 239 102 4960 12 168 96 4870 10 301	1 18 8 2 2	Clinical, symptomatic and hematological remission of 1 yr's duration Spleen not palpable—1 yr
8. Par F-42	11-17	1 Dizziness 2 Headache 3 Weakness 4 Plethora 5 Paresthesia of hands and feet 5 Backache	3 yrs 2 yrs	Phenylhydrazine and phlebotoxies for period of 2 yrs	1 Plethoric 2 Spleen—2 cm below costal margin 3 Enlarged thyroid 4 Palms of hands very red	128 6030	16	1200 3 4	M—H (differential findings within normal limits)	11-17-39 12-12-39 1-22-41	5 2 7 0 5 0 } (o) 18 1	3 6 9 12 15	02 3010 6 226 00 4200 6 90 02 4650 7 130 89 4150 6 481 83 4360 9 400	15 15 3 6 14	Clinical, symptomatic and subjective im- provement Occa- sional headaches, but no dizziness or paresthesia—1 yr Blood findings normal —1 yr Spleen not palpable—1 yr
9. Wer M-61	4-10	1 Headache 2 Weakness 3 Plethora 4 Blurred vision	3 yrs 2 mo	Numerous phlebotoxies for 1 yr preceding admission	1 Plethoric 2 Hands red 3 Retinal hemorrhages 4 Liver—1 cm Spleen—6 cm below costal margin	150 7800	17	400		4-14-40 7-6-40 7-7-40 7-25-40 10-15-40 12-17-40 1-6-41 1-10-41 1-23-41 3-12-41	6 5 2 9 2 8 5 7 } (o) 9 0 2 5 2 5 2 0 3 8 5 0 } (v) 42 7	3 6 9 12	147 6920 6 119 6525 8 440 134 6300 14 727 109 4980 7 310	14 1 1 3	Symptomatic and subjective remission— 6 mo Blood findings improved Spleen 2 cm below costal margin Liver not palpable
10. Wil F-65	8-12	1 Headache 2 Dizziness 3 Cyanosis 4 Weakness 5 Numbness of extremities	8 yrs	Phenylhydrazine and x radiation in 1932 Phle- botomies since	1 Plethoric 2 Spleen—7 cm below cost marg 3 Hands red 4 Retina—dusky hue, veins dis- tended and tortuous	153 8330	12	188 0.2	M—H (Diff findings within normal limits) Blood vol— 165 cc/kilo	8-21-40 9-16-40 10-1-40 12-16-40	10 0 10 0 12 0 6 0 } (o) 38 0	3 6 7	138 6700 12 150 140 6900 6 102 5020 5 142	20 6 10	Symptomatic and subjective improve- ment—6 mo Blood findings improved— 3 mo Spleen not palpable—3 mo

Polycythemic Patients

[illegible]

*** immeasurable**

TABLE II (Continued)

Periods after Intravenous Administration of Pz																					
	Name and Number of Patient Receiving Pz Both Orally and Intravenously	Interval in Days Between Oral and Intravenous Administrations	Name and Number of Patient Receiving Pz Intravenously	Microcuries of Pz Administered Intravenously	Milligrams of Sodium Phosphate in Which Pz Was Incorporated	2 Hours		6 Hours		24 Hours		48 Hours		96 Hours		Others		Time (Days) for Values Under "Other"			
						Total	%	Total	%	Total	%	Total	%	Total	%	Total	%				
Normal Individuals																					
Whole blood			Per 2	1500	600	0251	1673	0249	1660	0350	2330	0120	0800	0058	0386	0037	0240	8			
	R B C																				
	W B C																				
	Plasma																				
Whole blood			Vic 4	1500	600	0260	1733	0257	1713	0168	1120			0033	0220	0042	0280	8			
	R B C																				
	W B C																				
	Plasma																				

Polycythemic Patients

Whole blood	Wer 9	21	2550	167						0306	120	0212	083	0195	0764		
R B C stroma										—		—		—			
R B C										036	141	0518	203	0173	0679		
Plasma										005	0196	003	0118	005	0196		
Whole blood			6000	420					0495	0825	0755	0370	0617	0361	0602		
R B C stroma												00164	0027	00047	00078		
R B C									1260	210	217	0875	146	0602	100		
Plasma									0146	0243	0340	0130	0217	0083	0138		

Activities corrected for decay and to date of administration
Total amounts expressed in microcuries per c c , percentages in % of dose per 100 c c

TABLE III

Retention of P_{32} in the Phospholipid, Acid Soluble and Nucleoprotein Fractions of R B C, W B C and Plasma of Two Patients with Polycythemia (Expressed in μc per c c of R B C, W B C or Plasma)

Case No	Hrs after Adm	Amt (in Microcuries) of P_{32} Adm	Amt (in gm) of Sod Phos in Which P_{32} Was Incorp	Route of Adm	R B C			W B C			Plasma		
					Phospho	Acid S	Nucleo	Phospho	Acid S	Nucleo	Phospho	Acid S	Nucleo
9	24	2550	0 1785	Oral	0 0004	0 0212	0 0135	0 0042	0 0150	0 0026	0 0011	0 0018	0 0009
	48				0 0007	0 0188	0 0070	0 0022	0 0193	0 0110	0 0018	0 0032	0 0014
	96				0 0008	0 0172	0 0055	0 0099	0 0182	0 0145	0 0024	0 0018	0 0002
	— 21 Da				0 0012	0 0026	0 0007	0 0041	0 0045	0 0045	0 0015	0 0004	0 0002
9	24	2550	0 167	I V	0 0024	0 0399	0 0009	0 0115	0 0181	0 0028	0 0028	0 0022	0 0004
	48				0 0028	0 0276	0 0072	0 0221	0 0571	0 0092	0 0092	0 0018	0 0004
	96				0 0025	0 0051	0 0051	0 0370	0 0239	0 0043	0 0043	0 0016	0 0005
10	12	6000	0 420	I V	0 0010	0 124	0 0137	0 0103	0 1005	0 0155	0 0019	0 0113	0 0012
	24				0 0012	0 0930	0 0727	0 0224	0 1090	0 0233	0 0045	0 0076	0 0029
	48				0 0022	0 0900	0 0462	0 0219	0 1210	0 0511	0 0079	0 0055	0 0022
	96				0 0047	0 0486	0 0323	0 0091	0 0654	0 0450	0 0101	0 0017	0 0042

TABLE IV
The Retention of Radio-Phosphorus in the Stroma of Red Blood Cells

Case No	Amount (in microcuries) and route of P^{32} administered O = orally I V = intravenously	Days between adm and withdrawal of blood for fractionations	Amount of P^{32} in microcuries per 100 c c of packed R B C (Centrifuged 20 min at 1450 X gravity)	
			Hemoglobin Fraction -	Stroma
9	2500 (O)	1	977	immeasurable
		2	740	"
10	6000 (I V)	2	102	164
		4	745	0474
8	7900 (O)	21	492	0072
7	7000 (O)	22	672	0015

period (and probably during the 4 to 21-day period) while those of the acid soluble and nucleoprotein fractions decreased after the 24-48 hour period

(b) White blood cells The level of retention of P^{32} in the phospholipid fraction of the white blood cells of case 9 increased and that of case 10 decreased during the 96-hour period. Those of the acid soluble and nucleoprotein fractions appeared to reach a peak between the forty-eighth and ninety-sixth hour in both patients regardless of route of administration

(c) Plasma The level of retention of P^{32} in the phospholipid fraction of the plasma of the patients apparently reached a peak between the forty-eighth and ninety-sixth hours, while that of the acid soluble reached a peak

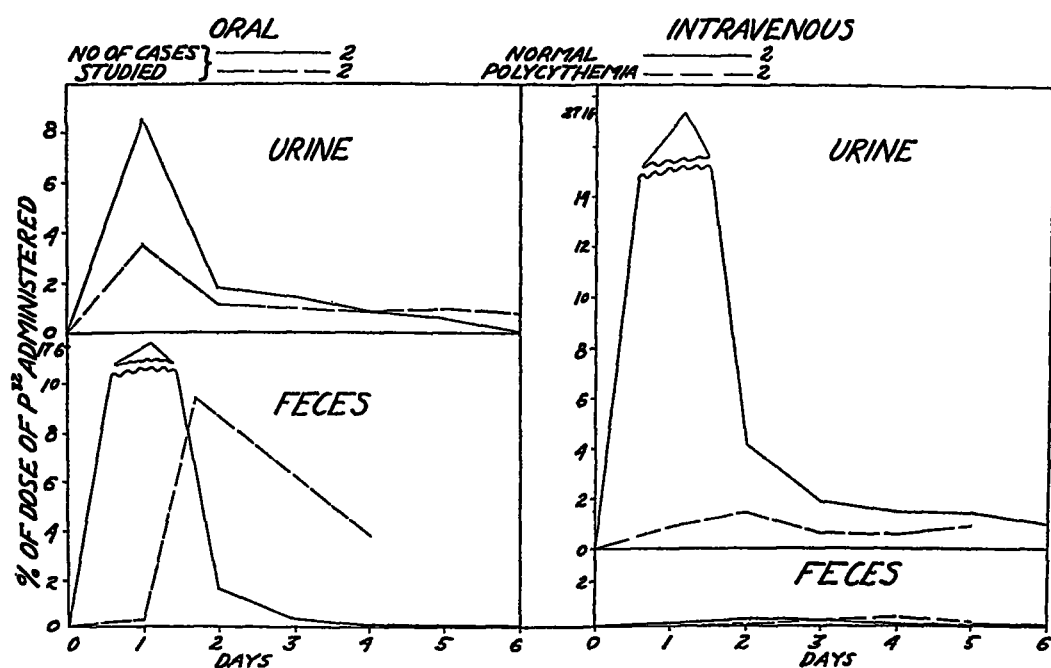


FIG 2 Average excretion of P^{32} in urine and feces of normal individuals and patients with polycythemia

TABLE V
Rates of Excretion of Radio-Phosphorus in Urine and Feces

Periods after Oral Administration of P ₃₂													Microcuries of P ₃₂ Ad- ministered Orally	Milligrams of Sodium Phosphate in Which P ₃₂ Was In- corporated	Name and Number of Patients Receiving Radio- Phosphorus Orally	
1 Day		2 Days		3 Days		4 Days		5 Days		6 Days		Total Excretion				
Total	%	Total	%	Total	%	Total	%	Total	%	Total	%	Total				%
Normal Individuals																
Urine	69.5	4.63	25.5	1.7	13.4	89	10.9	72	11.1	74	6.75	45	344	22.9	600	Mic. 1
Stool	194.0	12.93	7.8	52	3.32	22	41	02			95	06				
Urine	191.19	12.7	29.5	1.96	31.8	2.12	17.34	1.15	21.22	1.41	16.9	1.12	695	46.3	600	Rob. 3
Stool	338.98	22.59	38.8	2.59	5.85	39	3.05	10	14	01	18	01				
Polycythemic Patients																
Urine	35.76	6	17.88	3	11.92	2	11.92	2	25.96	1	25.96	1	1488	25.1	2800	Hay. 5
Stool			911.9	15.3			447.0	7.5								
Urine	173.0	6.79	56.9	2.23	23.3	91	43.4	1.70					400.96	15.7	178	Wer. 9
Stool	6.01	24	80.5	3.16	14.0	55	3.85	15								

TABLE V—Continued

Periods after Intravenous Administration of P ₃₂																					
	Name and Number of Patient Receiving P ₃₂ Orally and Intravenously	Interval in Days Between Be- tween Oral and Intra- venous Admin- istra- tions	Name and Number of Patients Receiving Radio- Phos- phorus Intra- venously	Micro- cures of P ₃₂ Admin- istered Intra- venously	Milli- grams of Sodium Phos- phate in which P ₃₂ Was Incorporated	1 Day		2 Days		3 Days		4 Days		5 Days		6 Days		Total Excretion			
						Total	%	Total	%	Total	%	Total	%	Total	%	Total	%	Total	%	Total	%
Normal Individuals																					
Urine			Per 2	1500	600	565 2	37 66	75 5	5 03	37 3	2 48	25 41	1 69	26 16	1 74	17 49	1 16	760	50 5		
Stool						1 47	098	3 87	25	3 72	24	2 49	16	35	02	77	05				
Urine			Vic 4	1500	600	250 0	16 66	52 5	3 5	22 6	1 5	22 2	1 48	19 11	1 27	16 0	1 06	391	26 1		
Stool						1 29	08	6 74	45					30	02	15	01				
Polycythemic Patients																					
Urine	Wer, 9	21		2550	167	25 6	1 00	58 8	2 31	36 8	1 44	23 2	91					164 97	6 46		
Stool						1 12	04	5 32	21	7 23	28	6 9	27								
Urine			Wilk 10	6000	420	Lost		63 7	1 06	13 9	23	47 0	78	74 1	1 23			251 4	4 18		
Stool						Lost		3 35	06	—		31 6	53	17 8	30			+	+		
Activities corrected for decay and to date of administration Total amounts and percentages of doses expressed in microcuries																					

Activities corrected for decay and to date of administration Total amounts and percentages of doses expressed in microcuries

before the forty-eighth hour, and that of the nucleoprotein fraction varied considerably

In case 9, to whom equal amounts of P^{32} were administered both orally and intravenously, the great majority of the fractionations of the blood retained proportionately more radio-phosphorus after its administration by the latter route

Table 4 indicates that very small quantities of radio-phosphorus are found in the stroma of red blood cells. In the few findings presented, there is apparently no distinct correlation between the concentrations of radio-phosphorus in the stroma and hemoglobin fractions in relation to the time element

Table 5 and figure 2 indicate the average per cent of the dose of administered P^{32} excreted in the urine and feces of normal individuals and patients with polycythemia. The normal individuals excreted from 25 to 50 per cent of the dose of P^{32} during the 6 days following its administration regardless of the route. However, during a period of 4 to 6 days the patients excreted less than 25 per cent of the dose. The patients excreted less P^{32} in both the urine and feces, regardless of the route of administration, than did the normal individuals

DISCUSSION

Radio-phosphorus, which emits beta-particles which can be accurately quantitated, can be used as a "tracer" or a therapeutic agent*. The beta particles have the capacity of producing ionization, just as do roentgen-rays, and therefore the effects of radio-phosphorus are fundamentally and basically similar to those of x-radiation. However, radio-phosphorus concentrates in bone marrow^{6, 7, 8} and since it has a half-life of 14.3 days it can constantly bombard with radiation a tissue, in which it concentrates, for many days. It is this latter feature that is probably responsible for the favorable hematological results obtained in the patients with polycythemia. In three of the patients (cases 6, 9 and 10) fairly large doses of radio-phosphorus had to be administered intravenously before a decrease in the hemoglobin levels took place. Presumably the concentration of P^{32} did not reach sufficiently high levels following oral administrations to reduce the production or release of red blood cells. The first evidence of significant decreases in the hemoglobin levels occurred approximately 100 days† after an effective dose (this depended upon the quantity and/or route of administration) of radio-phosphorus had been administered. Since radio-phosphorus has never produced

* The so-called "safe tracer dose" which has been studied in animals⁹ has not yet been studied in humans. Presumably, in the normal cases studied here, "radiation effects" have occurred and therefore accurate qualitative or quantitative deductions regarding phosphorus metabolism cannot be made.

It is known, from experiments upon both animals and human beings, that relatively large doses of sodium phosphate when accompanied with radio-phosphorus, reduce the amount of P^{32} retained by the blood. Therefore this variable would also alter deductions.

† The usual life span of an average human red blood cell

nausea, vomiting or any clinical ill effects after its administration this form of therapy seems acceptable at the present time. Perhaps other radioactive agents will be found to be superior. It should be reemphasized that the physical and clinical improvement of the patients was as remarkable as the hematological improvement.

If corrections for variations in blood volume, weight, etc. of the patients were made, the absorption levels would be different but the trends would be the same. Greater concentrations of P^{32} are found in the blood (and therefore the marrow) when radio-phosphorus is administered intravenously than when given orally.

The findings, presented above, of the fractionation of red blood cells are too incomplete to make deductions. However, it is interesting to note that the amounts of P^{32} found in the phospholipid fractions of the red blood cells of case 9 were much less than those of case 10. Since it is well known that the stroma of red blood cells is composed of substances lipoidal in character, it can be observed (tables 2 and 4) that the fraction containing the stroma of the red cells of case 9 retained immeasurably small amounts of P^{32} while that of case 10 retained approximately 1 per cent of all of the P^{32} of the red blood cells. This difference may be due to the increased quantity of P^{32} administered, to routes of administration, or even to differences in red cell or hemoglobin structure or production. It appears therefore that phosphorus ultimately reaches the stroma presumably after passing through the hemoglobin fraction. In general, however, less than 1 per cent of the P^{32} retained by red blood cells is found in the stroma.

The explanation is unknown for the lesser excretion of P^{32} from the patients with polycythemia than that from normal individuals. It can only be assumed that the tissues of the patients had greater need or affinity for the phosphorus or that the P^{32} was retained by the tissues for longer periods of time.

CONCLUSIONS

- 1 The distribution of P^{32} in various fractions of blood and the rates of excretion of P^{32} in the urine and feces of normal individuals and patients with polycythemia are presented.

- 2 Evidence is presented that marked clinical and hematological improvement in patients with polycythemia follows the administration of "therapeutic" doses of radio-phosphorus.

REFERENCES

- 1 LAWRENCE, J. H. Nuclear physics and therapy: preliminary report on a new method for treatment of leukemia and polycythemia, *Radiology*, 1940, **xxv**, 51.
- 2 LAWRENCE, E. O., and COCKSEY, D. On the apparatus for the multiple acceleration of light ions to high speeds, *Phys. Rev.*, 1936, **1**, 1131.
- 3 BERNSTEIN, S. S., JONES, R. L., ERICKSON, B. U., WILLIAM, H. H., AVRIN, I., and MACY, G. I. A method for the preparation of post-hemolytic residue or stroma of erythrocytes, *Jr. Biol. Chem.*, 1937-38, **cxii**, 507.

- 4 TUTTLE, L. W., SCOTT, K. G., and LAWRENCE, J. H. Phosphorus metabolism in leukemic blood, *Proc Soc Exper Biol and Med*, 1939, **xli**, 20
- 5 EISENMAN, A. I., ORI, L., SMITH, P., and WINKLER, A. A study of the permeability of human erythrocytes to potassium, sodium and inorganic phosphate by use of radioactive isotopes, *Jr Biol Chem*, 1940, **cxxxv**, 165
- 6 TUTTLE, L. W., SCOTT, K. G., and LAWRENCE, J. H. Studies on neoplasms with the aid of radioactive phosphorus II The phosphorus metabolism of the nucleoprotein, phospholipid and acid soluble fractions of normal and leukemic mice, *Jr Clin Invest*, 1941, **xx**, 57
- 7 LAWRENCE, J. H., SCOTT, K. G., and TUTTLE, L. W. Studies on leukemia with the aid of radioactive phosphorus, *New Internat Clin*, 1939, **iii**, 33
- 8 ERR, L. A. Clinical studies with the aid of radioactive phosphorus II Assay of radioactivity of tissues of patients dead of leukemia, *Jr Clin Invest* (In press)
- 9 TUTTLE, L. W., ERR, L. A., and LAWRENCE, J. H. To be published

EXPERIENCES IN THE TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS WITH SULFANILAMIDE, SULFAPYRIDINE AND SULFATHIAZOLE; A REVIEW OF PREVIOUSLY REPORTED CURED CASES WITH THE REPORT OF FIFTEEN TREATED CASES INCLUDING ONE CURE AND ONE ABORTED CASE *

By HOWARD E. HEYER, M D † and FORD K. HICK, M D , Ph D ‡,
Chicago, Illinois

THE advent of new chemo-therapeutic agents has provided the physician weapons with which to combat infectious endocarditis. While the majority of cases treated with sulfanilamide and its derivatives progress to a fatal issue, a definite minority have been shown to reach a stage of apparent clinical cure. Thirty-one cases which have been cured by the use of sulfanilamide and its derivatives have been gathered from the literature. For convenience the essential data have been collected in tabular form (chart 1). Undoubtedly, other additions will be made as chemotherapy becomes a more generally utilized means of treatment. In addition to the 26 cured cases listed below, Long and Bliss ¹ have reported five cases cured by sulfanilamide. Four of the five occurred in patients with congenital heart lesions. Because detailed clinical histories are not available, they have not been added to this collection.

The diagnosis of bacterial endocarditis is based on a well recognized clinical picture which needs no discussion. If one is to have confidence in it then certain postulations should be made. One should find in the patient a valvulitis or a congenital cardiac anomaly. If to this is added a positive blood culture, the case may be regarded as proved. If the blood culture is negative, splenomegaly with or without embolic manifestations is required to complete the diagnosis. In the cases of Major and Leger, and Kelson and White there was pathological proof of the cure, since the patients afterwards died of congestive heart failure and were examined post mortem. It is of interest to note that three of the 19 cases had congenital lesions, and 16 rheumatic valvulitis. In 12 cases *Streptococcus viridans* was recovered and in two a hemolytic streptococcus. In three patients the blood culture was sterile. The longest periods of observation at the time of the report were 15 and 18 months. Even though the periods of observation in the other cases were much shorter, the changes produced in the clinical pictures by the

* Received for publication March 15, 1941

From the University of Illinois, Department of Medicine, College of Medicine and Research and Educational Hospitals, Chicago, Illinois

† Resident Physician, Research and Educational Hospital

‡ Assistant Professor of Medicine, University of Illinois

treatment were sufficient to justify the assumption that a clinical cure had been accomplished. The accumulating evidence, therefore, suggests that in a few cases cures are being obtained and that ways and means may yet be found for making the sulfonamide derivatives more effective. For this reason the experience obtained in treating 15 cases over the last two and one-half years will be summarized. In addition to these, two cases will be reported in detail, in one a clinical cure was obtained and in the other a beginning valvular implantation seemed to have been aborted.

RESULTS OF TREATMENT

Fifteen cases have been treated by sulfanilamide, sulfapyridine or sulfathiazole, in the medical ward in the Research and Educational Hospital during the last three years. The series comprises seven women and eight

CHART I
Subacute Bacterial Endocarditis, Recovery from Therapy with
Sulfanilamide and Its Derivatives

Author	Patient Age-Sex	Blood Culture	Cardiac Diagnosis	Splenomegaly	Embolic Phenomena	Therapy	Period of Observation at Time of Publication
1 Klee, Römer ² 1935	* *	Sterile	Endocarditis	Present	*	Prontosil	8 weeks
2 McQuarrie ³ 1937	6 M	Streptococcus (type?)	R H D * with mitral sten and insuff	*	*	Prontylin	66 days
3 Hussey ⁴ 1937	34 M	Hemolytic strept	R H D with mitral and aortic stenosis	Present	Absent	Sulfanil	11 weeks
4 Major and Leger ⁵ 1938	39 F	<i>Strept viridans</i>	R H D with mitral and aortic insuff	Present	Present	Prontosil and sulfanil	Death from cardiac failure after 29 days of normal temperature
5 Manson-Bahr ⁶ 1938	60 M	Sterile	Endocarditis (R H D with mitral sten ? and possible aortic sten ?)	Absent	Absent	Prontosil	2 years
6 Manson-Bahr ⁶ 1938	45 M	Sterile	Endocarditis	Present	Absent	Prontosil	15 months
7 Major and Leger ⁷ 1939	36 M	<i>Strept viridans</i>	R H D with mitral sten and insuff	Present	*	Neo-prontosil, and sulfapyridine, and prontosil	1 year
8 Spink and Crago ⁸ 1939	18 F	<i>Strept viridans</i>	Patent ductus arter	Present	Present	Sulfanil	9 months
9 Barton and Stinger ⁹ 1939	4 F	<i>Strept viridans</i>	Prob congenital heart	Present	Present	Sulfanil	3 months
10 Kelson and White ¹⁰ 1939	22 M	Positive	*	*	*	Sulfapyridine and heparin	6 months
11 Kelson and White ¹⁰	23 F	Positive	R H D with mitral lesion	*	*	Sulfapyridine plus heparin	6 months Death from cardiac failure
12 Kelson and White ¹⁰ 1939	41 M	Positive	*	*	*	Sulfapyridine plus heparin	4 months
13 Andrews ¹¹ 1940	68 M	Sterile	Aortic insuff (etiol ?)	Present	Present	Sulfapyridine	

CHART I—Continued

Author	Patient Age-Sex	Blood Culture	Cardiac Diagnosis	Splenomegaly	Embolic Phenomena	Therapy	Period of Observation at Time of Publication
14 Lippman ¹² 1940	53 M	<i>Streptococcus viridans</i>	R H D (?)	Present	Present	Sulfanil neoprontosil and sulfapyridine with ammonium hepten-chlorarsenate (arsenical)	3½ months
15 Heyman ¹³ 1940	38 F	<i>Streptococcus viridans</i>	Patent ductus arter	*	Present	Sulfanilamide orally	18 months
16 Major ¹⁴ 1940	40 F	<i>Strept viridans</i>	R H D (?)	Present	Absent	Sulfapyridine	7 months
17 Christie ¹⁵ 1940	17 F	<i>Strept viridans</i>	R H D with mitral insuff	Present	Present	Sulfanil	1 year
18 Alexander S. ¹⁶ Alexander, S. F. ¹⁶ 1940	62 M	Hemoly strept	Mitral valvulitis	Absent	Absent	Sulfanil orally	4 months
19 Orgain and Poston ¹⁷ 1940	21 F	<i>Strept vir</i> and <i>N gonorrh</i>	*	Absent	Present	Sulfanil and Sulfapyridine	7 months
20 Bierman and Bachr ⁴⁶	32 M	<i>Strept vir</i>	Endocarditis	Absent	Present	Sulfanil and fever therapy	Over 2 years
21 Bierman and Bachr ⁴⁶	19 F	<i>B influenzae</i>	Endocarditis	Present	Present	Sulfanil and fever therapy	10 months
22 Solomon ⁴⁷	19 F	<i>Strept vir</i>	R H D with mitral sten and insuff	Present	Present	Sulfanil and typhoparatyphoid vaccine	18 months
23 Solomon ⁴⁷	40 M	Nonhemolytic strept	R H D with mitral and aortic sten and insuff	Present	Present	Sulfanil and typhoparatyphoid vaccine	2 months
24 Solomon ⁴⁷	19 F	<i>Strept vir</i>	R H D with mitral insuff and aortic sten and insuff	Present	Present	Sulfapyridine and typhoparatyphoid vaccine	5 months
25 Solomon ⁴⁷	14 M	<i>Strept vir</i>	R H D with mitral and aortic insuff	Present	Present	Sulfapyridine and typhoparatyphoid vaccine	2 months
26 Solomon ⁴⁷	37 M	Sterile	R H D with aortic sten and insuff	Present	Present	Sulfapyridine and typhoparatyphoid vaccine	2 months

(R H D = Rheumatic heart disease)

men the ages varying between 21 and 60 years. Thirteen patients were diagnosed clinically as rheumatic heart disease, one as a coarctation of the aorta, and one as hypertensive heart disease. Frequent hemoglobin determinations, and red and white cell counts were made. Blood levels of sulfanilamide, sulfapyridine and sulfathiazole were also determined in order to obtain maximum therapeutic concentrations. Blood cultures drawn were incubated for a period of three weeks before being pronounced sterile.

Chart 2 presents the essential data concerning treatment and its effects in tabular form.

CASE REPORTS

Case 8 A white female of Roumanian descent, aged 19, who had previously been well aside from slight dyspnea on stair climbing, was admitted on June 18, 1938, to the Research and Educational Hospital complaining of severe right lumbar

CHART II

No	Age-Sex	Cardiac Diagnosis	Splenomegaly	Blood Cultures	Embolic Manifestations	Total Medication	Duration Treatment	Results Treatment	Pathological Findings
1	28 F	RHD with mitral sten and regurg	Present	<i>Strept viridans</i>	Present	Sulfanilamide 37 gm	11 days	Death 9 mos	No postmortem
2	35 M	RHD with mitral sten and regurg	Present	<i>Strept viridans</i>	Present	Sulfanilamide 64.6 gm	18 days	Death 5½ mos	Mitral stenosis Vegetations on mitral valve "Septic spleen" Multiple infarcts
3	33 F	RHD with mitral insuff Mild diabetes	Present	Sterile	Present	Sulfanilamide 6.6 gm	4 days	Death 14 mos	No postmortem
4	23 M	RHD with mitral sten and insuff and aortic insuff	Present	<i>Strept viridans</i>	Present	Sulfapyridine 72 gm Sulfanilamide 6.6 gm	18 days 3 days	Death 3½ mos	No postmortem
5	31 M	RHD with mitral sten and insuff	Present	<i>Strept viridans</i>	Present	Sulfanilamide 38 gm	13 days	Death	No postmortem
6	31 F	RHD with mitral sten and insuff	Absent	<i>Strept viridans</i>	Present	Sulfanilamide 88.8 gm	24 days	Death 22 mos	Mitral stenosis Vegetations on mitral valve with ulcerations Multiple infarcts
7	36 M	RHD with mitral sten and insuff	Present	<i>Strept viridans</i>	Present	Sulfanilamide 26 gm Sulfapyridine 150 gm	9 days 47 days	Death 6½ mos	Mitral and tricuspid stenosis Vegetations on mitral valve Multiple infarcts Cerebral hemorrhage
8	21 F	Coarctation of aorta	Present	<i>Strept viridans</i>	Present	Sulfanilamide 58 gm	17 days	Clinical cure 2 yrs 9 mos	
9	27 F	RHD with mitral sten and insuff	Present	<i>Strept viridans</i>	Present	Sulfapyridine 81 gm	31 days	Death 6 mos	Mitral stenosis Vegetations on mitral, aortic and tricuspid valves Multiple infarcts
10	21 M	RHD with mitral sten and insuff and aortic insuff	Present	Sterile	Present	Sulfapyridine 97 gm Sulfathiazole 18 gm	31 days 6 days	Death	Mitral stenosis Vegetations on mitral valve Multiple infarcts
11	60 M	Hypertensive ht disease	Present	<i>Diplococcus pneumoniae</i>	Present	Sulfanilamide 16 gm	4 days	Death 1 mo	Vegetations on tricuspid and aortic valves Arteriosclerosis of aorta and coronary arteries
12	50 F	RHD with mitral sten and insuff	Present	Sterile	Present	Sulfapyridine 9 gm	5 days	Death 18 mos	Mitral and aortic stenosis Vegetations of mitral valve Multiple infarcts
13	35 F	RHD with mitral sten	Present	Sterile	Present	Sulfanilamide 30 gm Sulfathiazole 17 gm	5 days 3 days	Well during 5th mo	
14	32 M	RHD with mitral sten and insuff	Present	<i>Strept viridans</i>	Present	Sulfathiazole 82 gm	18 days	Alive during 4th month Some fever	
15	41 M	RHD with aortic sten and regurg, mitral sten and regurg	Present	<i>Strept viridans</i>	Present	Sulfathiazole 500 gm Sulfapyridine 120 gm	4½ mos 30 days	Alive during 8th month Some fever	

pain of six weeks' duration. This was accompanied by fatigue, weakness and weight loss. Six weeks before entrance the patient had a sudden sharp pain in the right lumbar region, accompanied by vomiting so severe as to cause her to "double up." She had spent three weeks at the Cook County Hospital (service of Dr. H. J. Isaacs) where a diagnosis of subacute bacterial endocarditis with a coarctation of the aorta was made. Two positive blood cultures, one of *Streptococcus viridans*, and one

of *Streptococcus hemolyticus*, were obtained there. The patient was discharged from the County Hospital with pain in the right kidney region unchanged, and fever.

The day preceding admittance to Research and Educational Hospital she had a severe chill lasting 10 minutes. The lumbar pain was very severe, accentuated during urination, and the urine was tinged with blood.

The past history included scarlet fever and pneumonia in childhood, measles, mumps, whooping cough and chickenpox, but no rheumatic fever or sore throats. The patient was poorly nourished, appeared acutely ill and in severe pain, holding the right side. On admittance she had a temperature of 101.6°, blood pressure 190 mm Hg systolic and 110 mm diastolic in both arms, pulse 134, respiration 26. The lungs were clear. The heart was enlarged slightly to the left, with a harsh systolic murmur at the apex, and a distinct, softer systolic murmur at the base, heard best at the third left interspace. Marked tenderness over the right lumbar area was noticed, but no muscle spasm.

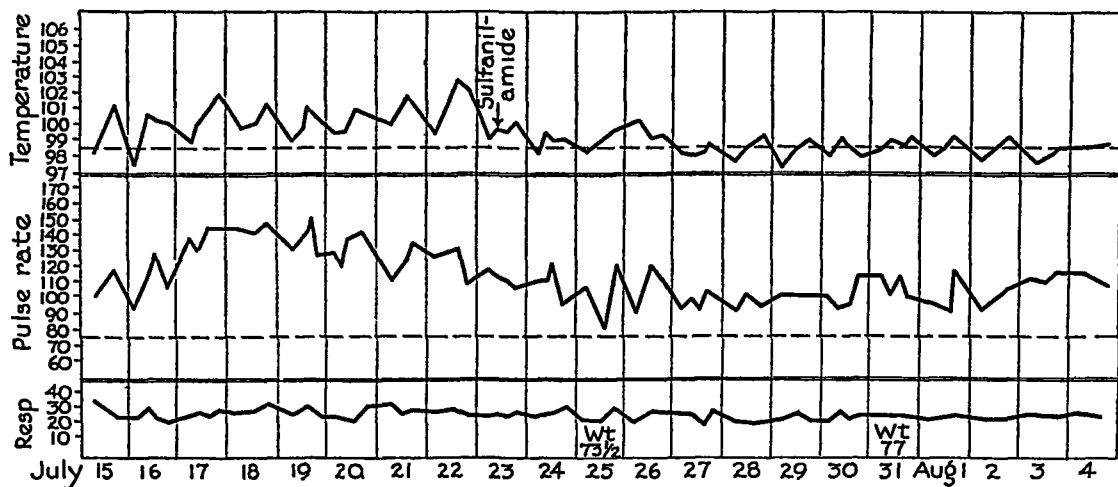


FIG 1

Femoral and dorsal pedal artery pulsations were not perceptible, and the blood pressure in the thighs could not be obtained.

The blood study revealed 11.5 gm of hemoglobin, 3,740,000 red cells and 19,500 white cells per cu mm. A catheterized specimen of urine contained innumerable red cells and many leukocytes. The blood also showed non-protein nitrogen 24 mg and urea nitrogen 12 mg. Roentgenograms of the chest revealed notching of the ribs, with a normal cardiac size and configuration.

Although the right lumbar pain diminished in the next 24 hours, the patient ran a septic temperature to 101–104° for five weeks. Splenic tumor was palpated on July 8. Blood cultures on July 7 and 15 revealed a *Streptococcus viridans*. On July 17 she complained of a severe pain in the left upper quadrant with local tenderness which was attributed to an infarct of the spleen. Rapid wasting brought her weight to 73 lbs on July 23.

On July 23 the patient was placed on 4 gm of sulfanilamide daily. The day sulfanilamide was begun, a marked drop in the fever occurred (see figure 1) and during the following 16 days this dose was continued. The fever disappeared, the patient improved markedly in strength and vigor, and gained 3½ lbs in weight. During sulfanilamide therapy the hemoglobin dropped from 10.7 gm to 7 gm, and the patient was given 400 cc of blood on July 30, 1939.

Two weeks after the initial dose of sulfanilamide, she was ambulatory and the spleen was no longer palpable. A total of 65.3 gm of the drug was given between July 23 and August 8.

Blood cultures obtained on August 9, 15, 17, 24 and September 12, revealed no growth of organisms.

The patient remained in the hospital until November 11, 1939 gaining in weight up to 93½ lbs, feeling well and exhibiting only occasional temperatures up to 99.2 to 99.6°. During the two years and nine months following the beginning of treatment the patient has remained well. She has been readmitted five times merely for purposes of observation. On one occasion, four months after treatment was stopped, a small hemolytic atypical streptococcus was isolated from the blood. Thirty-four blood cultures taken during the two years following, failed to show any growth of organisms. Splenomegaly and embolic manifestations have been absent, and the patient feels well in every respect.

When last heard from, the patient was leading the life of her people (being a gypsy) and was well enough to travel from Chicago to California by auto-trailer, without any ill effects.

This patient is of interest because of the long period of observation—two years and nine months—longer than any case treated with sulfanilamide previously reported in the literature that has come to our attention.

Case 13 M. B., a 35 year old nurse, single, was first admitted to the hospital on October 20, 1940 for treatment of an acute erysipelas of the right ear, cheek and neck, of 24 hours' duration. The tissues were edematous, raised, reddened, and large glands were palpable at the angle of the right jaw. The temperature rectally was 103.8° and the pulse 124 per minute. A mitral configuration of the heart with a presystolic thrill and murmur was found. No murmurs were audible at the base of the heart. The spleen was not palpable. The urine was clear, the white cell count 14,400 per cu mm.

The past history revealed three attacks of rheumatic fever during childhood and one of chorea. Pneumonia had occurred at 21 years, and a chronic sinus infection at age 28 years. An acute attack of pyelitis had occurred 4 years previously. For about 5 years she had suffered from chronic eczema of both external auditory canals.

Within 4 hours the fever had reached 106° rectally. The patient was given sulfanilamide by mouth, and was given a roentgen-ray treatment to the area of skin involved. She was also given 100 cc of convalescent scarlet fever serum intravenously. Her temperature then began to drop and by the third day was normal. Sulfanilamide levels of 71 mg and 47 mg were found on the morning of the second and third hospital days. Because of nausea, the sulfanilamide was stopped on the third day, after 13.3 gm had been administered. A blood culture drawn on the first hospital day was sterile. She was given a second and third roentgen-ray treatment to the affected region. She was discharged on the ninth hospital day with a diagnosis of erysipelas. At this time the local lesion was completely resolved.

On November 5, eight days after the previous discharge, she was readmitted with a similar lesion of the left ear, cheek and neck. The edema and redness were very marked, but the line of demarcation between diseased and blotchy skin was less pronounced than before. Large glands also appeared at the angle of the left jaw. The lungs were clear, the heart murmurs unchanged, the spleen was not felt. The temperature was 104° rectally on admission. Sulfanilamide was begun by mouth, and the patient was given 6.6 gm plus 4,000 cc of intravenous fluids and a roentgen-ray treatment during the first 12 hours. By the following day the temperature was 101.4° but the patient was very nauseated. She managed to retain 5.5 gm of sulfanilamide and was given 4,000 cc of intravenous fluids, and a roentgen-ray treatment. At

4 30 p m on the second hospital day, she developed a severe chill with an elevation in temperature to 104.5° rectally. At this time the heart seemed to be slightly enlarged and intravenous fluids were discontinued. One hundred c c of human scarlet fever convalescent serum were given intravenously. On the third hospital day the patient experienced a second and a third severe chill with the fever reaching 105.4° rectally. Intravenous administration of sulfanilamide was begun and 4 gm of the drug were given by vein. A second dose of 100 c c of convalescent scarlet fever serum was given and a third roentgen-ray treatment. The lesion over the left ear and cheek was much less reddened and swollen, and was definitely regressing. In spite of the improvement in the local skin lesion, the fever continued high and the chills persisted.

On the fourth hospital day evidences of pulmonary congestion appeared. Because of nausea, digalen was given subcutaneously and caffeine sodium benzoate intravenously. Slight cyanosis and icterus were noted. The patient was semicomatose and irresponsive. On this day 12 gm of sulfanilamide were given intravenously and the patient was given a 550 c c transfusion of blood. In spite of an adequate amount of fluid by vein, the temperature reached 106° rectally by evening. At this time the erysipelas had completely subsided.

On the fifth day the spleen was palpable for the first time. After 2 gm of sulfanilamide had been given intravenously without improvement, it was discontinued and sodium sulfathiazole begun in doses of 3 gm per 1000 c c of 10 per cent glucose, given as a slow drip by vein. From this time on, the temperature began to fall (see figure 3), and reached normal by afternoon of the sixth day. The improvement in her general condition was dramatic. During the sixth to the tenth hospital days the spleen was definitely palpable, two fingers below the costal arch, but by the twelfth day, was no longer felt.

On the fifteenth hospital day a faint reflux aortic diastolic murmur appeared for the first time. From the tenth to the twenty-first day the patient had temperatures reaching to 99.8° rectally, but the spleen was no longer palpable and at present, during the fifth month, she feels well. Five blood cultures taken since treatment have so far failed to show any growth.

During treatment sulfanilamide levels from 4.6 to 10.7 mg (total sulfanilamide) were obtained. Sulfathiazole levels varied between 1 mg and 3.85 mg. A total of 30 gm of sulfanilamide and 17 gm of sulfathiazole were given during the second admission.

Following the regression of the skin lesion the patient had remained desperately ill. The spleen had continued to enlarge and the sepsis was profound. It may be presumed that an implantation on the heart valve had occurred and that the persistent fever and splenomegaly were due to vegetations containing the hemolytic streptococcus. The development of the reflux aortic diastolic murmur during the period of her illness (it having been absent previously) is further evidence of acute valvular changes. The promptness with which chemotherapy was instituted after the illness began probably prevented extensive vegetative growths. The response to sulfathiazole, after sulfanilamide had failed to cause a remission, is of especial interest.

EFFECT OF TREATMENT ON FATAL CASES

Effect on Temperature Among the 13 remaining cases, the most marked and striking effect was the fall in temperature which followed the administration of these drugs. This drop in temperature was most marked

with sulfapyridine, but also occurred, although to a less marked degree, with sulfanilamide and sulfathiazole. Five cases were treated with sulfapyridine and three showed a prompt and rather marked decrease in temperature. The single case in which sulfapyridine did not result in a fall in temperature was moribund when therapy was begun. Of seven cases treated with sulfanilamide alone, six revealed a fall in temperature and one revealed a slight elevation in fever.

Of the five cases treated with sulfapyridine, two also were given a separate trial course of sulfanilamide, and two cases a course of sulfathiazole. Case 7 (chart 2) revealed a rise in temperature with the administration of sulfanilamide, followed by a fall below the previous level of fever when sulfapyridine was begun. Case 4 revealed a fall in fever with both sulfanilamide and sulfapyridine. Case 10, which had been originally treated with sulfapyridine with a decrease in fever, was treated with sulfathiazole beginning six days before death. The patient's temperature fell to normal levels within 48 hours, but he expired from inanition and circulatory failure on the sixth day of treatment. Case 13 revealed no change in the level of temperature with sulfanilamide, but had a prompt fall to normal levels with sulfathiazole.

Effect on Clinical Course of Fatal Cases The total duration of the fatal cases varied from one month to two years. The average duration of these cases was 8.9 months. This falls within the possible life expectancy of this disease and, as a group, no significant prolongation of life was found.

Case 7 gave the best clinical response among the fatal group, a complete remission of three weeks being produced. During this time the temperature was slightly elevated on only three occasions, and he gained in strength and was subjectively symptom-free. The ultimate outcome, however, was unaltered. With the exception of the transitory periods of fall in temperature, lasting a few days, the remaining cases were unimproved by treatment. Two patients were alive and still under treatment. The periods since the onset of their illness were four and eight months respectively. (Cases 14 and 15, chart 2.) Both cases continued to show both fever and splenomegaly at the time of publication.

Effect on Bacteremia All cases on whom blood cultures were drawn during treatment revealed a growth of organisms. This is at variance with the work of Spink and Crago⁸ who reported temporary sterilization of the blood in 6 of 12 cases treated with sulfanilamide. All the cases in this group that revealed a growth of organisms on culture before treatment, also revealed growth during treatment. The presence of sulfanilamide and its derivatives in the blood in therapeutic concentrations, therefore, did not render it sterile.

Case 10 revealed no growth at any stage of the disease, yet at postmortem, typical vegetations were found. Blood cultures from case 11 revealed a growth of *Diplococcus pneumoniae* following an attack of bronchopneumonia. This organism was resistant to sulfanilamide therapy.

Pathological Findings Seven of the 11 fatal cases were examined post-mortem, and at autopsy revealed typical vegetations, all with bacteria incarcerated beneath a fibinous covering. In six of seven cases the spleen was enlarged, varying in weight from 290 to 610 gm, and presented the pulpy, soft appearance associated with septic states. Numerous infarcts were also noted in the spleen, kidneys, lungs and liver.

COMMENT

The problem presented in the treatment of infectious endocarditis by means of chemotherapy concerns itself in large part with the susceptibility of the causative organisms to the type of chemotherapy chosen. Experimental proof of the importance of the strain of organisms found, in determining the response to sulfanilamide and its derivatives, is given by the work of Swain¹⁸ who found that *Streptococcus viridans* organisms isolated from two cases resistant to treatment with sulfonamide compounds were not inhibited by sulfanilamide, sulfapyridine or diaminosulfone in vitro. From the blood of two other cases which had a temporary remission with treatment, strains of *Streptococcus viridans* were isolated which were inhibited in growth in vitro. Osgood, Brownlee and Joski¹⁹ also found with in vitro experiments, that some groups of *Streptococcus viridans* were resistant to sulfapyridine, sulfathiazole and sulfamethylthiazole, while the growth of other groups was inhibited. Similarly, working with sulfanilamide in vitro, Bliss, Long and Feinstein²⁰ found 42 of 45 strains of *Streptococcus viridans* were inhibited in growth by the addition of sulfanilamide, while the remaining three strains were unaffected. The response to sulfanilamide compounds of the beta hemolytic streptococcus is well known, this may account for the success of treatment in case 2 (chart 1) treated by Hussey⁴ and in case 18 treated by Alexander,¹⁶ the beta hemolytic streptococcus being causative in each instance. Relative resistance of the pneumococcus to treatment with sulfanilamide has been noted by Long and Bliss,¹ and this is in accord with the fatal outcome in case 12 of this series (chart 2) where the pneumococcus was grown from the blood. Failure of sulfanilamide and sulfapyridine to cure pneumococcal endocarditis, has been previously noted by Terry,²¹ Fishkin,²² and Hollander.²³

The assumption, therefore, that patient 8 who recovered and patient 13 who was markedly improved, were infected with strains of organisms susceptible to the drugs used, seems likely.

The cause for the fall in temperature in the fatal cases which occurred during the administration of sulfapyridine and sulfathiazole, and to a lesser extent with sulfanilamide, has recently been clarified. Clinical observations on the depression of temperature in infectious endocarditis which occurred following the administration of sulfapyridine, have been made by Whitby,²⁴ Ellis,²⁵ Ravina²⁶ and Jones²⁷. The latter author noted a fall of the temperature to 94.0° during treatment with this drug. Beeson and Jane-

way²⁸ were able to demonstrate a fall of temperature below normal in rabbits after the administration of sulfapyridine. Lesser depressions were found with sulfathiazole and sulfanilamide. Fever produced in these animals by typhoid vaccine given intravenously was quickly abolished by sulfapyridine but not by sulfathiazole.

In cured cases the fall in temperature would seem to be due to sterilization of the blood stream and eradication of the infection. In the 11 fatal cases in this series, the blood was not sterilized, yet a fall in fever occurred in most cases. One may conclude that the temporary depression in temperature noted was in part due to the antipyretic action of the drugs used. Other investigators,⁸ however, have noted a temporary sterilization of the blood, and in these patients the fall in fever may be accounted for by control of the infection.

The incarcerated bacteria in the vegetations of subacute endocarditis remain as the major obstacle to treatment. Septicemia, due to streptococci without a complicating vegetative endocarditis, is capable of cure by chemotherapy^{29, 30}. It is believed that in case 13 the cure was accomplished or the disease aborted because the growth on the valves had not had an opportunity to accumulate significant fibrinous vegetations. When fibrinous material has appeared on the heart valves, cure is much more difficult. Kelson and White¹⁰ have reported three cases (numbers 10, 11, 12, chart 1) cured by heparin in conjunction with sulfapyridine. Friedman, Hamburger and Katz,³¹ Witts³² and Kleiber³³ have reported cases of subacute bacterial endocarditis unsuccessfully treated with heparin and sulfapyridine. Duncan and Faulkner³⁴ have demonstrated that the penetration of sulfapyridine and sulfanilamide, sulfathiazole and sulfamethylthiazole, into a previously formed clot was negligible. However, when these drugs were added to the blood before clotting occurred, a considerable amount of the drugs was found in the clot. Hence, if treatment is instituted very early in the disease, as the clot is forming, the possibility of destruction of organisms in the vegetation would seem likely. This would seem to have occurred in case 13.

From the work of Libman,³⁵ Capps³⁶ and Welch,³⁷ it is evident that spontaneous cure with healing of the vegetations may rarely occur. In assessing any cure, furthermore, a prolonged period of observation is necessary. Case 8 of the present group (chart 2) has been observed for two years and nine months following the beginning of treatment without relapse. This is a longer period of observation before report of a cure of subacute bacterial endocarditis (following treatment with sulfanilamide), than any that has previously appeared in the literature.

It is our belief that treatment with sulfanilamide and related compounds should be begun as soon as the diagnosis is made, and continued as long as possible. When no clinical improvement occurs with one of the sulfonamide compounds (as in case 13) another should be given a trial. With this form of therapy a minority of the cases will show improvement or cure, but this

fortunate group can be found only by clinical trial. With the remaining fatal group, remissions in some cases of varying length will probably occur.

SUMMARY

1 The clinical course of 15 cases of subacute bacterial endocarditis treated with sulfanilamide, sulfathiazole and sulfapyridine has been reviewed.

2 One of the cases has been cured and is alive and well two years and nine months after treatment was begun. A second case is alive at the time of writing, five months after the onset of illness, and has been apparently cured.

3 A collection of 31 previously reported cases of subacute endocarditis cured by sulfanilamide and its derivatives, has been gathered from the literature.

4 The use of sulfanilamide, sulfathiazole or sulfapyridine in all cases of subacute endocarditis seems warranted. Theoretically, the earlier the treatment is instituted, the better the chances are for cure.

BIBLIOGRAPHY

- 1 LONG, P. H., and BLISS, E. A. The clinical and experimental use of sulfanilamide, sulfapyridine and allied compounds, 1939, Macmillan & Co, New York.
- 2 KLEE, P. H., and ROMER, H. *Prontosil bei Streptokokkenkrankungen*, *Deutsch. med. Wchnschr.*, 1935, **1**, 253-255.
- 3 McQUARRIE, L. Report of cases treated with sulfanilamide, *Jr. Pediat.*, 1937, **x**, 188-194.
- 4 HUSSEY, H. H. Probable bacterial endocarditis apparently cured with sulfanilamide, *Med. Jr., Dist. Columbia*, 1937, **vi**, 275-276.
- 5 MAJOR, R. H., and LEGER, L. H. Recovery from subacute infectious endocarditis following prontosil therapy, *Jr. Am. Med. Assoc.*, 1938, **cx**, 1919-1921.
- 6 MANSON-BAHR, PHILLIP. Apparent cure of two cases with infectious endocarditis, *J. V. Chemotherapy Practitioner*, 1938, **cxviii**, 221.
- 7 MAJOR, R. H., and LEGER, L. H. Recovery from infectious endocarditis, *Jr. Kansas Med. Soc.*, 1939, **xxx**, 324-325.
- 8 SPINK, W. W., and CRAIG, F. H. Evaluation of sulfanilamide in the treatment of patients with subacute bacterial endocarditis, *Arch. Int. Med.*, 1939, **lxiv**, 228-248.
- 9 BARTON, R. L., and STINGER, DOROTHY. Subacute bacterial endocarditis treated with sulfanilamide, *Jr. Iowa Med. Soc.*, 1939, **xxix**, 402-404.
- 10 KELSON, S. R., and WHITE, P. D. A new method of treatment of subacute bacterial endocarditis, *Jr. Am. Med. Assoc.*, 1939, **cxiii**, 1700.
- 11 ANDREWS, C. T. Possibility of cure by sulfonamides with report of case treated with sulfapyridine, *Brit. Med. Jr.*, 1940, **i**, 5-8.
- 12 LIPPMANN, KURT. Subacute bacterial endocarditis (case), new method of treatment, *New York State Med. Jr.*, 1940, **xxx**, 524-528.
- 13 HEYMAN, JACOB. Subacute bacterial endocarditis successfully treated with sulfanilamide, *Jr. Am. Med. Assoc.*, 1940, **cxiv**, 2373-2375.
- 14 MAJOR, R. H. The effect of sulfanilamide compounds on endocarditis, *Am. Jr. Med. Sci.*, 1940, **clxxxix**, 759-768.
- 15 CHRISTIE, AMOS. Subacute bacterial endocarditis apparently cured with sulfanilamide, *Jr. Am. Med. Assoc.*, 1940, **cxv**, 1357-1358.

- 16 ALEXANDER, S, and ALEXANDER, S F Cure of a case of acute ulcerative endocarditis, Jr Am Med Assoc, 1940, cxy, 1712-1713
- 17 ORGAIN, E S, and POSTON, M H Gonococcal endocarditis with recovery after sulfapyridine, New England Med J, 1939, ccxvi, 167
- 18 SWAIN, R H A Strain variations in resistance of *Streptococcus viridans* to sulfonamide compounds (sulfanilamide, sulfapyridine and diaminosulfone), Brit Med Jr, 1940, i, 722-725
- 19 OSGOOD, E E, BROWNLIE, I E, and JOSKI, J Effectiveness of neoarsphenamine, mapharsen, sulfanilamide, sulfapyridine, sulfathiazole, and sulfamethylthiazole against *Streptococcus viridans*, Am Jr Med Sci, 1940, cc, 595
- 20 BLISS, E A, LONG P H, and FRINSTON, W H The differentiation of streptococci and its relation to sulfanilamide therapy, South Med Jr, 1938, xxxi, 303-315
- 21 TERRY, L L, and BLARD, E E Cure of Type XIV pneumococcal meningitis by sulfapyridine (sulfanilamide deriv) confirmed by autopsy, case (with endocarditis), Am Jr Med Sci, 1940, clxxxix, 63-67
- 22 FISHKIN, B G, and PILOT, I Fatal tricuspid endocarditis treated with sulfapyridine, Illinois Med Jr, 1940, lxxvii, 244-247
- 23 HOLLANDER, A, and LANDSBERG, E Acute endocarditis due to an anaerobic pneumococcus, Jr Lab and Clin Med, 1940, xxvi, 407-311
- 24 WHITBY, LIONEL Chemotherapy of bacterial infections, Lancet, 1938 ii, 1095-1102
- 25 ELLIS, DONALD G Treatment of subacute bacterial endocarditis with M & B 693, Lancet, 1938, ii, 1521-1523
- 26 RAVINA, A Sulfapyridine action on evolution of maligendocarditis lenta, Bull e mem Soc méd d hôp de Paris, 1939, lv, 40-41
- 27 JONES, C O Subacute bacterial endocarditis, report of a case, South Med and Surg, 1939, ci, 602-603
- 28 BEESON, PAUL B, and JANEWAY, CHAS A The antipyretic action of sulfapyridine, Am Jr Med Sci, 1940, cc, 632
- 29 CHRISTIE, W B Recovery from *Streptococcus viridans* septicemia, Med Rec, 1937, cxxxvi, 489
- 30 KRUSEN, F H, and BENNETT, R L Unsuccessful treatment of subacute endocarditis with combined fever and sulfanilamide therapy, Proc Staff Meet Mayo Clin, 1940, xv, 328-332, Correction, 352
- 31 FRIEDMAN, M, HAMBURGER, W W, and KATZ, L N Use of heparin in subacute bacterial endocarditis, a preliminary report, Jr Am Med Assoc, 1940, cxiii, 1702-1703
- 32 WITTS, L J Heparin in subacute endocarditis, Brit Med Jr, 1940, i, 484
- 33 KLEIBER, E Subacute bacterial endocarditis unsuccessfully treated with sulfapyridine and heparin, Jr Am Med Assoc, 1940, cxv, 1713-1714
- 34 DUNCAN, C N, and FAULKNER, J A Penetration of blood clot by sulfanilamide, sulfapyridine, sulfathiazole and sulfamethylthiazole, Am Jr Med Sci, 1940, cc, 492-494
- 35 LIBMAN, E A consideration of the prognosis in subacute bacterial endocarditis, Am Heart Jr, 1925, i
- 36 CAPPS, J A Subacute bacterial endocarditis due to *Streptococcus viridans* with special reference to prognosis, ANN INT MED, 1939, xiii, 280
- 37 WELCH, F E, and SOUTHWOOD, A R Apparent cure in a case of subacute bacterial endocarditis, Med Jr Australia, 1939, i, 392-394
- 38 MAEGRAITH, B G, and VOLLUM, R L The bacteriostatic effects of Sulphonamide-P, Soluseptasine and M & B 693, Brit Med Jr, 1938, ii, 985-986
- 39 KINELL, J, and ERNSTEIN, A C Subacute endocarditis treated unsuccessfully with sulfapyridine, Cleveland Clin Quart, 1940, i, 83-86
- 40 ROSENTHAL, A H, and STONE, F M Puerperal infection with vegetative endocarditis Report of sulfanilamide therapy in two fatal cases due to *Streptococcus hemolyticus* Groups B and C, Jr Am Med Assoc, 1940, cxiv, 840-843

- 41 BAYLIS, T B, and LEWIS, W H Subacute bacterial endocarditis in older people, ANN INT MED, 1940, xiii, 2154-2163
- 42 FOLFY, J A, and YASUNA, E R Sulfanilamide in treatment of erysipelas, Jr Am Med Assoc, 1940, cxv, 1330
- 43 MIDDLETON, W S, and BURKE, M *Streptococcus viridans* endocarditis lenta, Am Jr Med Sci, 1939, cxviii, 301-323
- 44 ABBOTT, M A S Atlas of congenital cardiac disease, Am Heart Assoc, 1936
- 45 WECHSLER, H F, and GUSTAFSON, EINAR Coarctation of the aorta (adult type), congenital bicuspid aortic valve, subacute bacterial endocarditis, Am Heart Jr, 1937, xiv, 107
- 46 BIERMAN, W, and BAEHR, G The use of physically induced pyrexia and chemotherapy in the treatment of subacute bacterial endocarditis, Jr Am Med Assoc, 1941, cxvi, 292-294
- 47 SOLOMON, H A Subacute bacterial endocarditis, treatment with sulfapyridine and intravenous injections of typhoparatyphoid vaccine, New York State Jr Med, 1941, xli, 45-50

THE AMERICAN BOARD OF INTERNAL MEDICINE AS A FACTOR IN SCHOLARSHIP IN AMERICAN MEDICINE¹

By ERNEST E. IRONS, M.D., F.A.C.P., *Chicago, Illinois*

IT is now five years since the American Board of Internal Medicine was organized. In this period a total of 2,449 have been certified, 624 of these by examination. It is perhaps salutary again to review the objectives of such certification as the Board conceives them, and to look ahead to anticipate, if possible, some of the requirements of the medical leaders of the coming years. The Board recognizes that it is only one of the agencies concerned in efforts to improve the quality of medical care and scholarship. All those who participate in programs of graduate education, whether in preparation for certification by the various boards, or under other auspices, state or local, do so voluntarily, and the programs are designed to meet the needs and abilities of the several categories of physicians. The years of preparation for examination for certification are years of growth and of further development of orderly and thorough habits of study and thought. The examination is a necessary method of determining whether candidates have attained a degree of medical information and experience likely to ensure their future continued growth in medical knowledge and scholarship.

Much concern has been expressed over the large proportion of graduates in medicine who are seeking to become specialists, but already in some sections there is evidence that the trend of medical graduates is increasingly toward general practice. Realization of the expenditure of time and effort necessary to qualify the physician in a specialty is also likely to limit the number of candidates to those who are willing to work hard and long, and who in addition feel the urge to excel in some field of medicine. However, there always will be need for physicians with additional training in the more specialized branches of medicine. It is the task of the Boards to see to it that those who enter the specialties with their approval, shall be fully qualified.

While there are a number of incidental aims and satisfactions for the candidate which derive from the passing of the examinations, such as the completion of one of the qualifications for membership in the College of Physicians, the personal sense of satisfaction of having passed a milestone in one's career, or the attainment of a measure of approbation of one's colleagues, the Board is more interested in the fact that the candidate has embarked on a career of study voluntarily, and has thereby expressed the desire to excel, and to participate personally in the world's progress in medicine.

The successful student of the future, as in the past, must have good health, good principles, good tools, and the will to work. The quality of

¹ Read at the Boston meeting of the American College of Physicians, April 21, 1941

the student's training in secondary school and college has much to do with supplying him with effective tools for his medical studies. A sound classical education, which at the moment seems to be a little out of style, should supply him with usable tools in Latin, French, German and Spanish, and, most important, a knowledge of English grammar and ability easily to express his thoughts in good English. Chancellor Carmichael of Vanderbilt University in discussing the contribution of liberal education to professional studies has reemphasized the importance of sound fundamental education as a preparation for successful prosecution of later professional training. Some knowledge of Latin and Greek is necessary to understand terms, and of French and German for access to the literature of the more recent past and present. *Foreign language study gives the American student a knowledge of his own language, a precision of expression, and hence precision of thought.* These educational acquisitions are more important at the preparatory college level than is factual learning, and provide the attitude of mind, and the perspective sense of values essential to him who aspires to achieve real success in a learned profession.

I am aware that it may appear unseemly for a physician to voice criticism of certain current educational methods practiced in some colleges and secondary schools. But contacts with a considerable number of earnest and industrious medical students, and with young ambitious physicians, as well as experiences in the examinations of the Board, lead to the conclusion that in many instances the evident scholastic deficiencies are not due entirely to lack of industry or of professional guidance, but to faults in early education in secondary schools. No doubt great improvement has been made in methods of teaching a number of the subjects in the curriculum of secondary schools, but judging from results the teaching of English has shared least in this improvement.

In a recent discussion of the use of texts in High Schools it was stated that in the High Schools of one large city, 20 per cent of the children admitted from the grade schools had not sufficient command of English to be able to read and understand the material set forth in the High School texts. It may be argued, of course, that the great masses of children in public schools make it impossible to insist on much more than a rudimentary knowledge of reading, writing, and arithmetic. But the same conditions of superficial teaching of English exist in many private elementary and secondary schools. The recognized achievements of "Progressive Education" do not seem to have included thorough drill in the elements of English. Ability to think is made effective by ability accurately to express one's thoughts. "Usage" is but a poor substitute for an early and thorough analytical study of grammar and sentence structure. The student of medicine, thus ill prepared, manages to limp through such English as he is obliged to take in college. Later in the medical school, he wonders why at examination time his instructors fail to appreciate his efforts to demonstrate his knowledge in writing.

No matter what form of practice the medical student aspires to, he needs a basically sound preliminary education. A good general knowledge of world history will stabilize his fundamental thinking. The mental training afforded by mathematics, and a sound knowledge of the sciences, especially physics, chemistry, and biology, will make much easier the difficult and crowded years of his medical course, and later will sharpen his critical sense in the evaluation of medical problems and conclusions.

The secondary school and college preparation of medical students, as indeed that of all students entering professional careers, varies widely in quality. Those students whose early preparation is defective may still recover lost ground, and reach high attainments later, but this will be only at the expense of time and greater effort when all their energies should be directed toward the mastery of the medical curriculum.

General medical education is now much more uniform in quality than is secondary and college education, but even in medical education there is great divergence in the qualities of preparation of students and in the inspiration offered by the several schools. And even if schools were all on a par, there would still be a wide variation in quality of performance of individual students. Medical students like other people have differing mental endowments and differing ideals and personalities. The requirements in the practice of medicine, beyond the minimum standards for licensure and the safe care of the sick, vary according to locality and the type of work to be undertaken. The American Board is primarily interested in encouraging men to go further educationally than the minimum legal requirements. Such additional training should not unfit them for the practice of medicine, but should make them better, safer doctors, whose medical life will be brightened by the pleasure of participating in the advances and the scholarship of medicine. From such a group must come the qualified leaders of the future.

The necessity of research in medicine is self evident. Vast sums are devoted to the promotion of a multitude of projects. Some of this effort is barren, but now and then a new fact, or method, or principle, is established which justifies the entire expenditure. Some of this research is carried on by men who are well prepared also in clinical medicine. Other equally important and sometimes more fundamental research is carried on in internal medicine by men whose progress would be impeded rather than helped by insistence that they acquire also the degree of clinical experience demanded of candidates for the American Board of Internal Medicine. For such specially endowed research minds, other scholastic goals and rewards are available. The field of the Board of Internal Medicine is thus not all-inclusive.

The Board deplores the tendency of some of the younger men to regard the successful passing of the Board's examination as an end in itself rather than as an indication of the acquirement of another section of preparation for a life work. Out of this misconception of the ultimate aims of the Board come several rather unfortunate attitudes of medical students. In-

ternships in hospitals are of various lengths and content of experience arranged to suit the peculiar needs and available facilities of hospitals, and in some cases to comply with state laws. Many of the better hospitals hold that a rotating internship of one year affords but a smattering of experience, and that to be effective for the hospital and especially for the intern who contemplates general practice, a rotating internship should be at least two years in duration. While the internship may repair mistakes and fill gaps left by an inadequate medical curriculum, this is not its primary purpose. Rather should it be regarded as affording a period of growth in an orderly program of continuing education. If the service offered is confined to fewer departments of medicine, an adequate intern experience may be acquired in a somewhat shorter time. The prospective intern, however, feels that he must get on with his formal preparation for the Board and desires to cut his internship to the minimum one year, so that he may proceed with his residency, forgetting that what he needs is experience, which may be as well or frequently better attained in the two year internship than in some short internships and residencies. The attempt thus to save time and to come up for examination in the minimum allowable period may result in an inferior preparation, and in some cases failure of the candidate.

Further it is difficult to see how coaching in the ordinary sense can be of any material benefit to the candidate. Preparation must be based on years of continuous thoughtful study free from the inhibitions of stereotyped questions, or of conformity to any one rigid program of training. The questions asked by the Board are designed to determine whether the candidate has a broad knowledge of the fundamental facts of medicine. It is evident that the few questions asked can afford only a sampling of this knowledge. Some questions have been criticized as being of the nature of catch questions, or questions which stray from the beaten path of information in common use. The employment of an occasional question of this kind has been deliberate and purposeful, in order to explore the extent of the candidate's collateral information. Final judgment is based not on one question but on his general ability and knowledge as demonstrated by the examination as a whole.

The young physician has already spent at least eight years in his preparation for medical practice. How can the suggestion for another five year minimum of preparation be justified? Viewed as a requirement for practice it evidently cannot be justified, either legally or economically. The first eight years are required in satisfaction of the demands of the police power of the State. Anything further is entirely voluntary on the part of the physician. The justification therefore must come from the physician's own willingness to work, in order to acquire a superior knowledge of his subject, and in his hope that he may contribute something to the sum of human knowledge, or that in any case he may have the satisfaction of superior accomplishment in the care of the sick. Many excellent and able physicians quite properly will not feel that they can, or should, devote further time to

formal study. Others will desire to obtain additional preparation, and for these, certain suggestions as to residencies, supplementary study in the basic medical sciences, or the less formal but frequently effective preceptorship are offered. The American Board believes that such programs, or similar ones, will be useful guides to perhaps the majority of candidates, although the Board recognizes that other plans may be equally effective. The test of any program will be the results achieved by the candidate. In outlining such programs for those who wish advice, the Board hopes to assist the candidate to avoid inferior and superficial plans which may lead to failure and disappointment in later years, at a time when the golden opportunity for growth is past.

Just as candidates voluntarily apply to the Boards for examination, so the Boards themselves are voluntary in their organization and should restrict their activities to the setting and maintenance of standards. Any pronouncement by the special Boards, suggesting that their certificates be made a requirement for membership on hospital staffs is to be deprecated. Such a pronouncement would interfere seriously with the influence of the Boards in promoting medical scholarship. If hospitals, or other civic or state organizations, see fit to utilize the information as to standards of professional ability afforded by certificates of the Boards, that is a matter of their local policy. It should never be imposed on them by the Boards. The function of the Boards is to establish standards of achievement. By the nature of their organization, they have no authority, nor were they intended to have power, to enforce their standards on anyone.

The physician's choice of his career in medicine will depend on his inclination, his ability, his opportunity, and his preparation. His preparation, including his premedical education, will influence his inclination, and if faulty, will limit the opportunity to which his ability might otherwise entitle him. Habits of thoroughness and the willingness to work are essential.

Into whatever sphere of medicine he enters, the effective doctor should maintain a scientific attitude toward disease, and at the same time that of humanity toward the patient. The science of medicine must be combined with a large element of human sympathy and understanding, as Morgagni put it—the resolve “to be useful to mankind.”

CASE REPORTS

HISTOPLASMOSIS OF DARLING, REPORT OF A CASE*

By ROBERT B. WRIGHT, M.D., and FRANK W. HACHTEL, M.D.,
Baltimore, Maryland

HISTOPLASMOSIS is a rare, anatomically widely disseminated, usually fatal fungus infection often characterized by fever, anemia, leukopenia and splenomegaly. The condition is caused by *Histoplasma capsulatum* which may be found in large numbers in the reticulo-endothelial cells and may be cultivated from the blood and other tissues. No specific therapy has been found. Mantell et al., as reported by Meleney,¹ used a pentavalent antimony preparation (Neostam) possibly with some success.

The fungus, *H. capsulatum*, has two forms. One is yeast-like and occurs in the blood and reticulo-endothelial cells. The other, the mycelial form, is assumed when it is grown outside the body. This fungus has been well described by DeMonbreun.²

Blood cultures in infusion broth incubated at 37° C show both types. When such cultures are plated out on blood agar and kept sealed at 37° C colonies of both forms will develop. On blood dextrose agar plates made from the patient only the mycelial type of colony has been described.

The mycelial form alone grows on cultures held at room temperature. Its development is enhanced by the use of media adjusted to a pH of 6.5 with hydrochloric acid. The growth is white and cotton-like. Numerous aerial hyphae develop. The mycelia are highly refractile, straight, branched and segmented. Aerial spores 10 to 25 microns in diameter (as shown in figures 1 and 2) appear about the end of one week.

On blood agar the colonies of the mycelial type usually do not show aerial hyphae. They are reddish-brown and blend with the surrounding media.

The yeast-like form grows only on blood or serum agar at 37° C. The colonies are brownish-white, elevated, round and resemble those of bacteria. In young cultures the organism is oval and approximately 3 to 3.5 microns in diameter. Budding is often seen. The individual cells possess a thin membrane which surrounds a cytoplasm containing one or more fat droplets and often a protoplasmic granule in active Brownian movement. The cell tends to be partially decolorized by Gram's method.

The fungus has never been found outside the animal body and has only been isolated from man and the dog.³

When injected into suitable animals the mycelial form causes an abscess from which the yeast-like type can be cultivated on blood agar. If this latter form is injected intravenously lesions develop similar to those described in man.

* Received for publication April 4, 1941.

From Departments of Pathology and Bacteriology of University of Maryland School of Medicine, Baltimore, Maryland.

TABLE I

Author	Year	Place	Positive Cultures	Organism Round in Blood Smears	Organism Round in Biopsies	Organism Found at Autopsy in							Various Organs
						Lung	Liver	Spleen	Nodes	Adrenals	Intestine	Marrow	
Clemens and Barnes Dodd and Tompkins Forty and Cumbertson by Meleney Hansmann and Schenken Reid, Scherer and Irving	Sept 1938	Ky	Blood			++	++	++	++		++	+	Viscera Skin Kidney
	1932	Tenn	Blood	+		++	++	++	++		++	+	
	1934	Ind	Biopsy and blood			++	+	+	+	+	+	+	
	1939	D C	Skin ulcers	+		++	+	+	+		+	+	
	Feb 1938	Va	Blood			+	+	+	+		+	+	
Wright and Hachtel	1938	Md	Blood			+	+	+	+				Heart and nasal septum
Agress and Gray ¹⁷ Almeida and Lacaz	1939 1939	Mo Brazil	Skin		+	+	+	+	+		+		
Amolsch and Wax ¹⁸ Crumrine and Kessel ¹⁹ Darling	1939 1931 1906	Ohio Calif C Z		+	+	++	++	++	++		+		
Darling Darling Gunter and Lafferty ²⁰	1908 1908 1940	C Z Pan Ala				++	++	++	++		+		
Humphrey Humphrey Mantell et al by Meleney	1940 1940 1940	Mich Mich Fla			++	+	++	++	++				Heart, pancreas, kidney Kidney

TABLE I—Continued

Author	Year	Place	Positive Cultures	Organism Found in Blood Smears	Organism Found in Biopsies	Organism Found at Autopsy in						
						Lung	Liver	Spleen	Nodes	Adrenals	Intestine	Marrow
Martin and Silber by Meleney ¹ Meleney Meleney	1939 1939 1939	Calif Tenn Tenn				+++	++	+		+		
Moore and Blanche by Meleney ¹ Muller ²¹ Negrom	1939 1940	Mo Java Arg	Skin ulcer			+			+		+	
Parsons by Meleney ¹ Parsons Phelps and Mallory	1940 1926	Mich Mich Hon	Nose ulcer			+				+		
Riley and Watson ²² Shaffer, Shaul and Mitchell ²³ Vilela and Para by Meleney ¹	1926 1939 1940	Minn Va Brazil				+	+++	++	++	+	+	+
Wade by Meleney ¹ Weller by Meleney ¹ Williams and Cromartie	1926 1940	P I Ohio Tenn			+				+			Skin, viscera Pharyngeal ulcer and epiglottitis

Thirty-one cases of histoplasmosis have been found in the literature Darling ^{4, 5, 6} reported three cases and Humphrey ⁷ two Meleney ¹ collected 11 previously unpublished cases and added two of his own The others have been reported singly.

Among the 31 cases reported (table 1) there have been 24 autopsies In a few of the postmortems the organism was not widespread Phelps and Malloy ⁸ found it in the air passages only. The case of Parsons reported by Meleney ¹ showed "Histoplasma-like" organisms in one adrenal in a patient with generalized tuberculosis In a case of leukemia reported by Williams and Ciomartie ⁹ it was found in pharyngeal ulcers, the epiglottis and cervical nodes In one instance Meleney found the fungus only in the lungs

H capsulatum has been isolated in culture in eight cases In two instances (Parsons ¹⁰ and Negroni ¹¹ the organism was obtained from ulcers alone and no information as to the outcome is available Hansmann and Schenken ¹² grew the fungus in the antemortem cultures of cutaneous ulcers and then found it in the tissues both at biopsy and necropsy They classified this organism as belonging to the genus *Sepidonium* Most writers since have considered this case as histoplasmosis DeAlmeida and Lacaz ¹³ cultivated the fungus from a biopsy of the skin and found the organism in sections The four remaining cases (Dodd and Tompkins ¹⁴, Forry as reported by Meleney ¹, Clemens and Barnes ¹⁵ and Reid et al ¹⁶ had positive blood cultures and exhibited the parasites in many organs at autopsy To the present total of five cases from which *H capsulatum* was isolated and later found disseminated in the organs at necropsy the writers wish to add another

CASE REPORT

The patient, a white male, bartender, 59 years old, was last admitted to St Joseph's Hospital on the service of Dr E H Benson, February 9, 1939 He had had two previous admissions, April 30, 1936 and April 11, 1937 During the patient's first hospital stay it was found that he had diabetes mellitus which was treated by diet and insulin in the usual manner and he was discharged after 17 days His second admission was because of an extensive suppurative process in the calf of the left leg Incision liberated much pus from which a staphylococcus was isolated The diabetes mellitus was controlled by diet and insulin and he was discharged after 33 days Three weeks prior to the last admission he had had attacks of sharp grinding epigastric pain which was worse after a meat meal Some relief was obtained by belching gas There was no nausea or vomiting During the three weeks he had had a hacking cough, night sweats followed by chills and a constant frontal headache Examination revealed an emaciated, febrile, very ill man The skin presented a distinct icteric tint His heart was rapid No abdominal tenderness or rigidity was elicited but a mass was felt in the region of the gall-bladder The second toe of the left foot was discolored and appeared partly gangrenous

Laboratory Blood Wassermann, negative

Blood counts	2/9/38	2/10/38	3/2/38
Hemoglobin	65%		72%
White blood cells	2,500	4,850	2,500
Red blood cells	4,250,000		4,300,000
Polymorphonuclear	75%		74%
Lymphocytes	23%		26%
Mononuclear	2%		

Icteric Index 2/17/38—3, 3/4/38—12

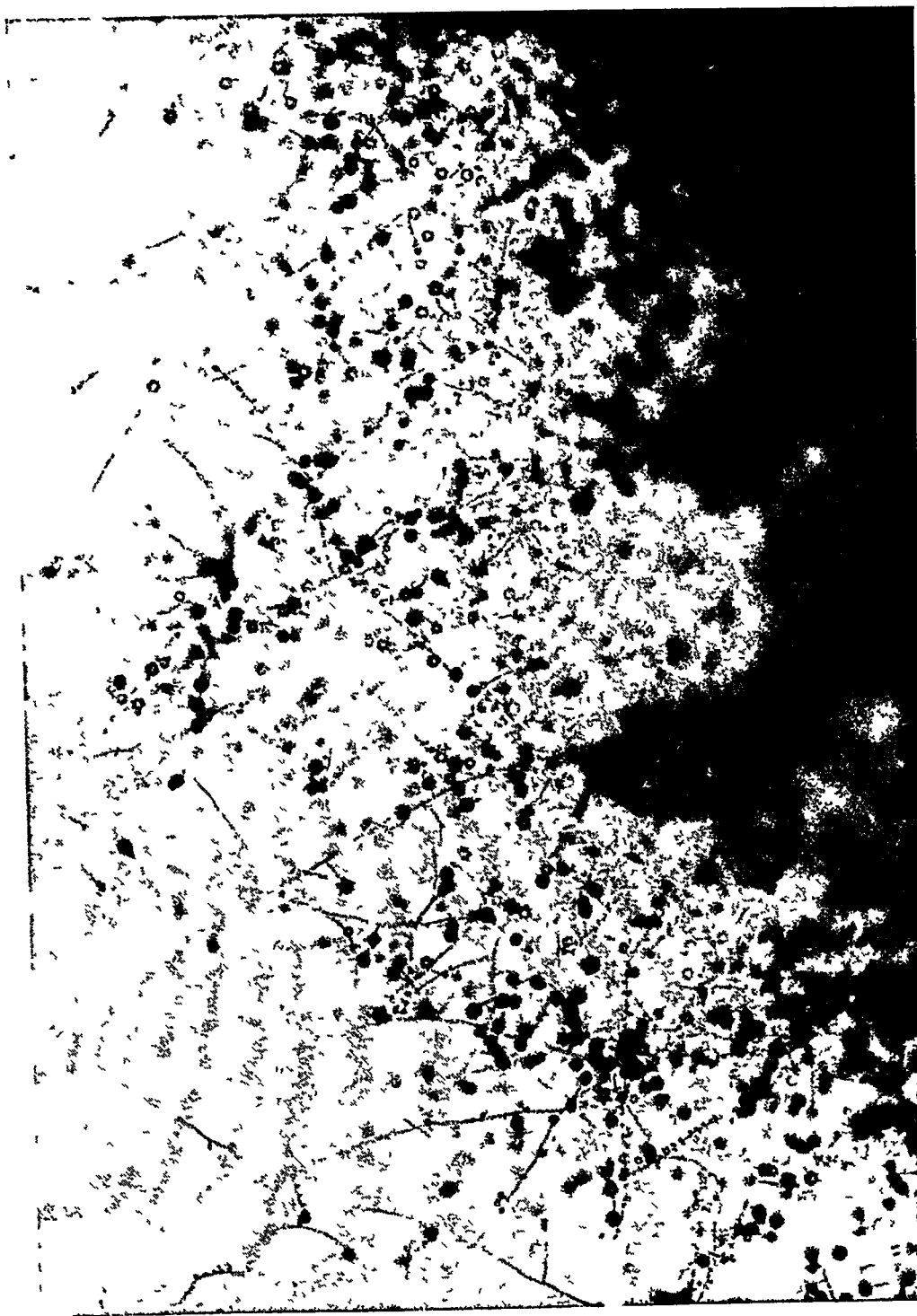


FIG 1 Colony showing aerial hyphae bearing numerous aerial spores $\times 150$



FIG 2 Higher magnification Tuberculated appearance of aerial spores $\times 930$

Blood non-protein nitrogen was normal. There was marked variation in blood sugar. On a constant diet and insulin dosage it varied from 105 to 190 mg per cent.

Serum agglutination for typhoid, paratyphoid, tularemia and undulant fever was negative.

A gastrointestinal examination by roentgen-ray failed to reveal any significant lesions.

By roentgen-ray the gall-bladder was considered pathological. Roentgen-ray of the chest was interpreted as showing bronchitis.

The patient ran a septic course with fever ranging from 95° to 103° F. There were frequent sweats and the diabetes was hard to control.

On March 14, 1938 an exploratory abdominal operation was done under local anesthesia. The liver was found to be nodular. The head of the pancreas and the regional nodes were hard and nodular. A node was removed for examination. The patient became weaker, temperature was below normal, pulse was rapid, skin clammy, urine contained sugar when the blood sugar was 125 mg per cent.

The lymph node was 2 cm in diameter and had a homogeneous gray, opaque cut surface. Sections showed its architecture to be greatly altered by large areas of necrosis surrounded by a thick zone of conspicuous phagocytic cells containing as many as 25 bodies 3 to 4 microns in diameter. The bodies had a small basic staining central portion around which there was a clear zone. Each organism had a sharp margin which strongly suggested a capsule.

The section of the lymph node was interpreted as histoplasmosis and led to the taking of blood cultures on March 17 and 18. The patient died on March 19, 1938. The organism (figures 1 and 2) developed in the cultures after five days' incubation and was found to be morphologically like that described by DeMonbreun.

At autopsy the body was examined by a member of the house staff who stated that it was emaciated and presented a recent right rectus wound held together by silk sutures. There were many pleural adhesions but no fluid in the pleural sacs. The lungs were soft and contained many small focal lesions suggestive of tubercles. The spleen weighed 500 grams and contained many isolated gray nodules 2 mm in diameter. The liver was pale and weighed 3000 grams. Its capsule was smooth and had a gray color mottled by pale brown. The lobular markings were not evident on the cut surface which presented an appearance similar to that seen through the capsule. The kidneys weighed 250 grams each. They had granular surfaces after the capsules were removed. The cortex and pyramids showed no definite abnormality. The gall-bladder and stomach showed no significant abnormality. Unfortunately the pancreas was not examined.

Section of the lung shows marked distortion of the alveolar architecture near the pleura by fibrous tissue. There are irregular spaces which contain a papillomatous structure covered by columnar epithelium. The abnormal tissue described above can be followed to the pleura where there is a marked deposit of granulation tissue in which one finds many lymphocytes and large phagocytic cells containing organisms morphologically like those described above. In the deeper pulmonary tissues there are sometimes found clumps of large apparently phagocytic cells but in no instance do they contain the organisms which are so numerous in the pleural zone. In the spleen there are frequent areas of necrosis around which large cells containing bodies similar to those seen in the lymph nodes and pleura are found in moderate numbers. The organisms do not appear as numerous in the spleen as in the lymph node. The portal zones of the hepatic lobules are very large and tend to have a sharp margin. They contain considerable fibrous tissue and lymphocytes as well as many large cells similar to those seen in the lymph node. In most of the lobules the only organisms found are in the portal zones. In a few places actual necrosis is found. Here there are many more parasite-laden cells immediately around the necrotic tissue. These cells can be fol-

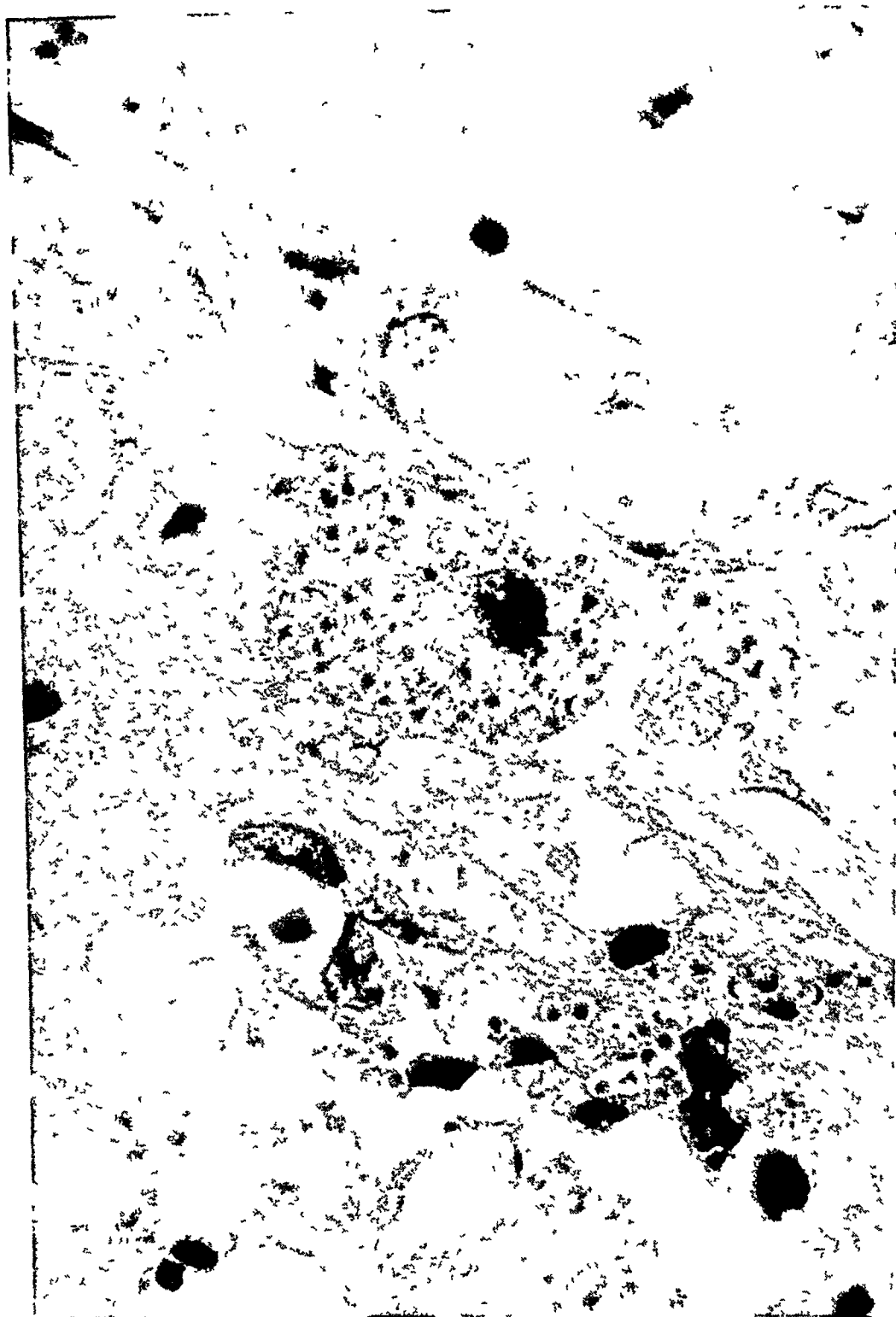


FIG 3 Oil immersion Large mononuclear cells in a lymph node There are innumerable parasites

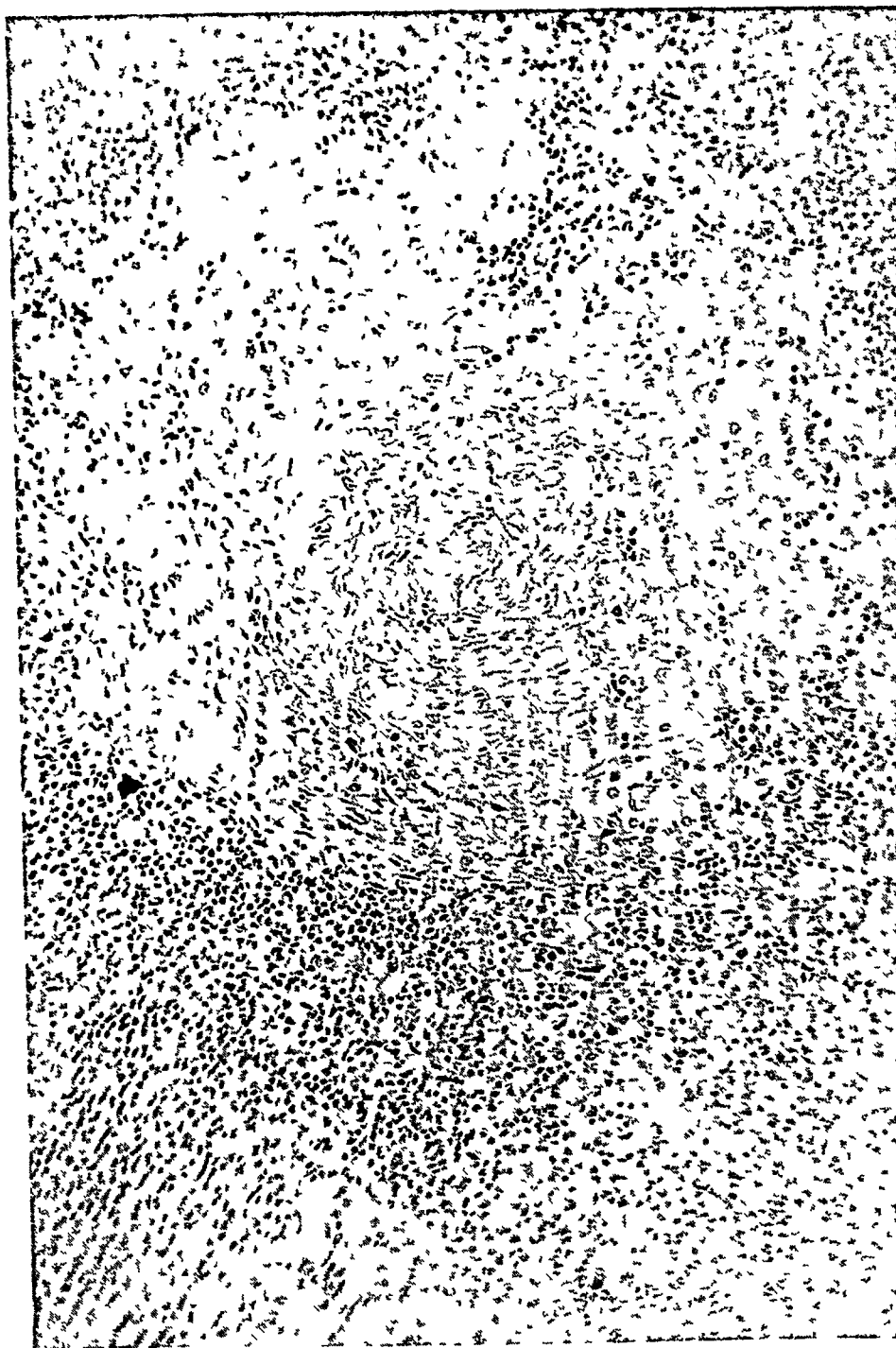


FIG 4 Spleen A focal area of necrosis around which large cells containing organisms can be seen

lowed for some distance in the blood sinuses around these necrotic areas. No organisms can be found in the sinuses except near the portal areas and areas of necrosis. Sections of the heart and kidneys failed to show any organisms or other significant lesions.

The usual hematoxylin and eosin stain after formaldehyde fixation showed the intracellular forms better than Gram's stain (MacCallum's method), Giemsa's stain or acid fast stain.

The mycelial form of these organisms obtained from blood cultures of the patient was injected subcutaneously in a Rhesus monkey. An abscess developed at the site. This was aspirated and cultured on blood agar at 37° C. Then the yeast-like form thus obtained was injected into the veins of a second monkey. The second monkey became ill but after several months seemed to recover. During his illness blood cultures showed *H. capsulatum*. After months he was killed and at autopsy many small old abscesses were found in the lungs. These abscesses had purulent centers and a fairly definite fibrous tissue wall. No organisms could be demonstrated at autopsy either by sections or cultures. Further study of the pathogenicity of this organism is contemplated.

SUMMARY

1. A case of histoplasmosis in a bartender and diabetic is reported. This is the second case in which the diagnosis was made before death.

2. The diagnosis can be made only by finding the organisms in stained smears or sections or by cultures. It may be suspected in a case of continued fever, anemia, splenomegaly and leukopenia.

3. The organism will grow in ordinary nutrient broth or on blood agar. It requires at least five days to develop.

4. Tissues fixed in formaldehyde and stained by hematoxylin and eosin show the intracellular form of the fungus well.

5. The yeast-like form was injected into a Rhesus monkey and several times *H. capsulatum* was obtained from the blood stream of the monkey. The animal recovered and at autopsy no organism could be found.

6. The disease may not be generalized and does not appear to be always fatal. Treatment by pentavalent antimony is mentioned by Meleney.

The authors wish to express their gratitude to Dr. E. H. Benson for permission to report this case.

REFERENCES

1. MELENEY, HENRY E. Histoplasmosis (reticuloendothelial cytomycosis) a review, *Am Jr Trop Med*, 1940, xx, 603-616.
2. DEMONBREUN, W. A. The cultivation and cultural characteristics of Darling's *Histoplasma capsulatum*, *Am Jr Trop Med*, 1934, xiv, 93-125.
3. DEMONBREUN, W. A. The dog as a natural host for *Histoplasma capsulatum*, *Am Jr Trop Med*, 1939, xix, 565-587.
4. DARLING, S. T. A protozoon general infection producing pseudo-tubercles in the lungs and focal necroses in the liver, spleen and lymph nodes, *Jr Am Med Assoc*, 1906, xlv, 1283-1285.
5. DARLING, S. T. Histoplasmosis a fatal infectious disease resembling Kala-Azar found among natives of tropical America, *Arch Int Med*, 1908, ii, 107-123.

- 6 DARLING, S T The morphology of the parasite (*Histoplasma capsulatum*) and the lesions of histoplasmosis, a fatal disease of tropical America, Jr Exper Med, 1909, vi, 515-531
- 7 HUMPHREY, A A Reticuloendothelial cytomycosis, Arch Int Med, 1940, lxxv, 902-918
- 8 PHELPS, B M, and MALLORY, F B Toxic cirrhosis and primary liver cell carcinoma complicated by histoplasmosis of the lung, United Fruit Co Fifteenth Annual Report, Department of United Fruit Co, 1926, 115-122
- 9 WILLIAMS, R H, and CROMARTIE, W J Histoplasmosis, report of a case, ANN INT MED, 1940, xiii, 2166-2171
- 10 PARSONS, R J Transformation of the mycelial form of *Histoplasma capsulatum*, Darling, to the yeast-like form in mice (Society Transaction), Arch Path, 1940, xxix, 731
- 11 NEGRONI, PABLO Mycologic study of the first South American case of histoplasmosis, Proceedings Third International Congress Microbiology, 1940, 508-509
- 12 HANSMANN, G H, and SCHENKEN, J R A unique infection in man caused by a new yeast-like organism A pathogenic member of the genus *Sepidonium*, Am Jr Path, 1934, x, 731-738
- 13 DEALMEIDA, F, and LACAZ, CARLOS, S Cogmuelo do genero histoplasma isolado de lesoes de cromomicose Associacao de fungos nas lesoes, Folia Clin et Biol, 1939, xi, 65-69
- 14 DODD, KATHERINE, and TOMPKINS, EDNA A case of histoplasmosis of Darling in an infant, Am Jr Trop Med, 1934, xiv, 127-137
- 15 CLEMENS, HARRY H, and BARNES, M L Histoplasmosis of Darling, Report of a case, South Med Jr, 1940, xxxiii, 11-15
- 16 REID, J D, SCHERER, J H, and IRVING, H Histoplasmosis in U S, Science, 1940, xci, 264, and private communication
- 17 AGRESS, H, and GRAY, S H Histoplasmosis and reticuloendothelial hyperplasia, Am Jr Dis Child, 1939, lvii, 573-589
- 18 ANOLSCH, A L, and WAX, J W Histoplasmosis in infancy Report of a case, Am Jr Path, 1939, xv, 477-481
- 19 CRUMRINE, R M, and KESSEL, J F Histoplasmosis (Darling) without splenomegaly, Am Jr Trop Med, 1931, xi, 435-449
- 20 GUNTER, W A, and LAFFERTY, C Histoplasmosis of Darling, Jr Med Assoc Alabama, 1940, ix, 337-339
- 21 MULLER, H Histoplasmosis in Oost Java, Geneesk Tijdschr v Nederl Indie, 1932, lxxii, 889-895
- 22 RILEY, W A, and WATSON, CECIL J Histoplasmosis of Darling, Am Jr Trop Med, 1926, vi, 271-282
- 23 SHAFFER, FRANK J, SHAUL, JOHN F, and MITCHELL, R H Histoplasmosis of Darling, Jr Am Med Assoc, 1939, cxiii, 484-488

Since submission for publication, the following articles have come to the attention of the authors

- CONANT, N F A cultural study of life-cycle of *Histoplasma capsulatum*, Darling, 1906, Jr Bact, 1941, xli, 563-580
- PARSONS, R J The histopathology of histoplasmosis in man, Proc Am Assoc, Path and Bact, Am Jr Path, 1941, xlvii, 582-584
- RHODES, P H, CONANT, N F, and GLESNE, L R B Histoplasmosis, report of case in infant 3 months of age, Jr Pediat, 1941, lviii, 235-241

LATE TULAREMIC SEPTICEMIA: RECOVERY FOLLOWING ADMINISTRATION OF SULFANILAMIDE COMPOUNDS ¹

By LESTER M MAY, M D , *San Antonio, Texas*

TULAREMIA is an increasingly common disease, carrying with it, in severe cases, a definite mortality. Curtis¹ has reported on the use of sulfanilamide in tularemia. The following case represents another and somewhat earlier usage of sulfanilamide compounds.² The case is of further interest in that it displayed several unusual diagnostic features. The clinical course was rather more severe than in Curtis' case, while the recovery following specific drug therapy was quite as rapid and as definite.

CASE REPORT

M M, a white male aged 21 years, was admitted to the Sinai Hospital December 9, 1936 in a semi-comatose state. He was employed in the kitchen of a local hotel as chief poultry and game dresser. Rubber gloves were not worn in this work. One year before, another kitchen employee had contracted what was diagnosed as "rabbit fever." Six days before admission, the patient had skinned and quartered six rabbits, but did not cut or bruise himself in so doing. Three days before admission, he went to bed feeling well, but awoke suddenly with violent shaking chills. Severe and almost constant frontal headache, generalized aching, and ten shaking chills occurred within the next 24 hours. This same day, he noted that the entire terminal phalanx of the third finger of the left hand was painful, reddened, swollen and tender. Seven shaking chills occurred on the day before admission. Sore throat, an occasional dry cough, and a localized area of pain, tenderness and swelling in the left axilla were noted this same day. On the evening before admission, the inflammation of the third terminal phalanx appeared to subside, but the terminal phalanx of the fourth (ring) finger of the left hand now began to show similar inflammatory changes. The patient vomited and had a rather copious epistaxis on the morning of admission. No other skin lesions of any sort had been noted.

On admission, he appeared acutely ill, and was occasionally disoriented and incoherent. The temperature was 105° F, the pulse 105, the respiratory rate 26. The blood pressure was 110 systolic, 80 diastolic. Several shaking chills occurred during the examination. The terminal phalanges of the third and fourth fingers of the left hand were tender, red and swollen, there were no skin abrasions or ulcerations, nor were any other dermal lesions visible. In the left axilla a firm, smooth, exquisitely tender acorn-size lymph node was palpated. There were a few shotty, non-tender nodes at the jaw angles, but no other palpable nodes. The eyes were clear externally. A small amount of dried blood was present just within the nares, and the upper nasopharynx contained several large masses of dried blood. The lower pharynx was moderately and diffusely reddened. A few coarse rhonchi were heard in both interscapular regions after cough, the lungs were otherwise clear to percussion and auscultation. The splenic edge was felt at the left costal margin. The neck was held slightly extended. Babinski's sign on the right was equivocally positive.

Admission laboratory findings revealed hemoglobin 88 per cent, erythrocytes 4,800,000, and leukocytes 12,000, polymorphonuclears 80 per cent, lymphocytes 18 per cent, monocytes 2 per cent. The examination of the urine was negative. A throat

* Received for publication April 23, 1940.

From the Medical Service of Dr. Charles R. Austrian, Physician-in-Chief, Sinai Hospital, Baltimore.

The drugs used in this case were Prontylin and Prontosil, supplied by the Winthrop Chemical Co., New York City.

swab showed no pneumococci. Spinal fluid drawn on admission was found to be under normal pressure and clear, the Pandy test was negative, 8 mononuclear cells were found, and a culture proved negative. Blood culture, taken on admission, and cultivated on routine blood agar media, showed no growth. A blood Wassermann test was negative, and blood sugar and blood urea levels were within normal limits. Admission roentgen-ray of the chest was interpreted as normal.

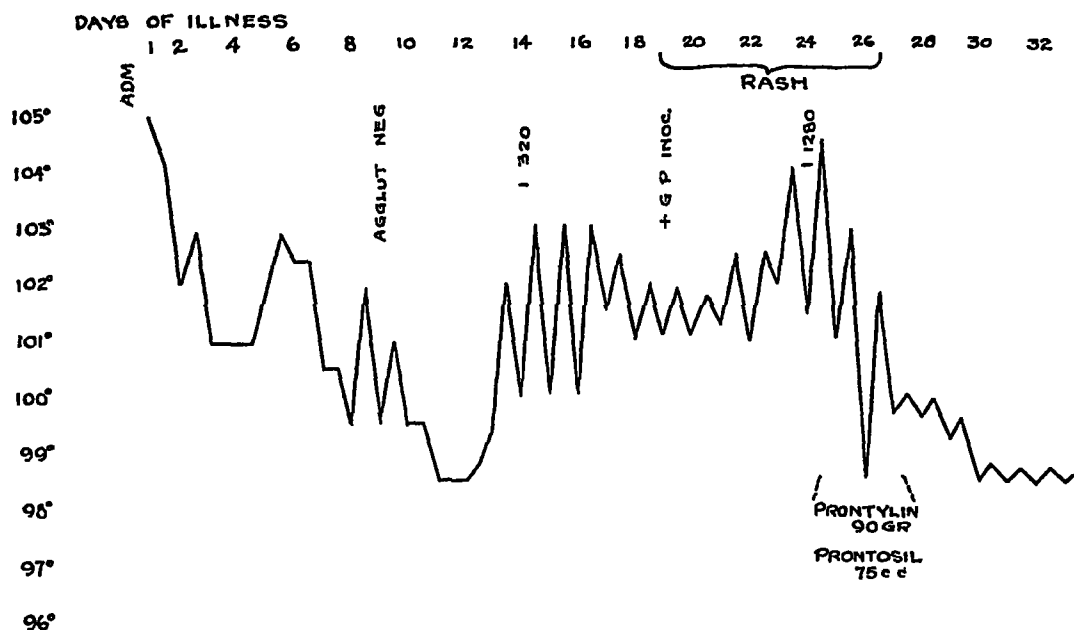


CHART 1 Temperature graph indicating rapid termination of septic curve following institution of drug therapy

The inflammatory swelling of the two terminal phalanges, as well as the swelling of the axillary node, subsided completely within the first few days. The spleen was not palpable two days after admission. Repeated blood cultures were taken, and inoculated on routine blood-agar media, all showed no growth. The lungs remained clear. He soon became better oriented, but still appeared rather toxic during the first week. Agglutinations on December 18 were negative as well as those performed on admission. Agglutinations on December 23 were positive for *B. tularensis* in 1:320 dilution. Temperature and pulse fell to normal by slow lysis, and the general condition gradually and markedly improved. However, on December 21 a secondary intermittent fever began and persisted, spiking daily to 102–103° F. At the same time, he again appeared quite ill showing the general signs of toxicity and impaired sensorium seen on admission, although in slightly less degree. On December 28, a peculiar blotchy rash appeared over the tibiae, patellae, and elbows—erythematous and quite symmetrical. This rash became tender on the next day, and subsided completely by January 5. On the day of the rash's first appearance, a guinea-pig was inoculated with freshly-drawn blood, and showed signs of tularemia five days later—conjunctivitis, lymph node enlargement, and smears positive for *B. tularensis* from conjunctival fluid and urine. By January 2, the patient's blood titer for *B. tularensis* had reached 1:1280.

On January 2, treatment was started with Prontylin gr 5 every 3 hours, and 5 c c Prontosil solution every four hours intramuscularly. A total dosage of 90 gr of Prontylin and 75 c c of Prontosil was given over a three day period. A dramatic drop in temperature occurred on the second day—the first fall in 12 days. A secondary rise occurred that night, but the temperature came down and remained down.

for the rest of the hospital stay. Protitylin dosage was increased to gr 15 every 4 hours on January 3. Treatment with Protitylin and Protosil was discontinued on January 5.

During the entire stay in the hospital, the urine remained clear, and the leukocytes ranged between 9000 and 12,000, averaging 70 per cent polymorphonuclears, and 30 per cent lymphocytes. He was discharged afebrile and cured on January 24.

COMMENT

Francis² states that a satisfactory and successful method for obtaining laboratory evidence of blood stream invasion by *B. tularensis* is to inoculate guinea-pigs with blood taken from patients during the first to twelfth days of the illness. The guinea-pig is then examined for evidences of tularemia, or its tissues are inoculated on artificial media containing cystine. In a review of the literature, he reports on 52 cases in which guinea-pig inoculation was positive for *B. tularensis*. Of these, five positive inoculations came from blood drawn during life. He states "Blood taken during life, after the first week of illness, was always negative except that one case yielded a (positive) culture on the twelfth day." Hitch and Smith,³ in a comprehensive review, comment that bacteremia in tularemia always ceases by the fourteenth day. They state "Repeated inoculations of guinea-pigs with patients' blood have never given positive results later than this." Therefore, the septicemia in this case must be regarded as occurring at, or persisting to, an unusually late date, since a positive blood inoculation was here obtained on the twenty-second day of the illness.

The primary lesion in this case, a diffuse inflammatory cellulitis of two adjacent terminal phalanges, was also distinctly unusual. The clinical duration was only five days. Perret,⁴ in a clinical review of 69 cases, describes the primary lesion of the "ulcero-glandular" type of tularemia as being a "small, superficial, indolent ulcer." Wooley,⁵ reporting on typical lesions of experimental tularemia in laboratory animals, describes the microscopic appearance of skin lesions (following scarification and puncture), as that of a diffuse, rapidly necrotic ulceration. Francis,⁶ Goodpasture and House,⁷ and other observers uniformly describe ulceration as the single type of primary tularemic lesion. A search of the literature revealed no previous reports of any similar variation from the classical type of primary lesion.

The dermal manifestations, too, were unusual, although it is known that tularemic skin rashes have a protean character. The skin involvement here resembled clinically the type sometimes seen in pyogenic septicemias, such as the painful, tender erythema overlying an early metastatic pyogenic osteomyelitis. In the opinion of Hitch and Smith,³ tularemic eruptions are primarily a toxic, rather than a bacteremic or septicemic manifestation. They point out that many patients show the cutaneous eruptions when relatively afebrile. However it is of interest to note that in this case the rash came on concomitantly with a secondary rise and spiking of temperature, and at this time the patient again appeared quite ill and was occasionally disoriented. This second clinically septic period was demonstrated to be concurrent with blood stream invasion by tularemic organisms. It would appear, therefore, that the eruption described here could more properly be termed "septic" rather than "toxic." The figures of Hitch and Smith give the average duration of tularemic rash as about 22 days. In this case, the rash lasted only eight days. It is possible that this short duration may have been due

to the administration of the sulfanilamide compounds, these were begun on the fifth day of the rash, at which time the skin lesions were quite florid

The prognostic significance or seriousness of septicemia in tularemia is difficult to evaluate, clinical data upon this subject in the literature are meager. In a review of autopsied cases reported by Gundry and Warner,⁸ only 4 of the 14 reviewed cases included results of premortem animal inoculation of patients' blood. In all of these four cases, the animal inoculations were positive for *B tularensis*. Postmortem animal inoculations were positive in all cases in which this procedure was carried out (7 out of 14). No conclusions are to be drawn from these figures, they are suggestive rather than conclusive. However, on the basis of the severe clinical relapse associated in this case with proved blood stream invasion by *B tularensis*, there would at least be reason to assume that tularemic septicemia, particularly when occurring late in the course of the disease, should be regarded with as much gravity as septicemia in the more common pyogenic infections.

SUMMARY

A wide variety of treatments has been used in severe or complicated cases of tularemia, ranging from phenol locally to salvarsan intravenously, this would seem to indicate that no really dependable therapeutic agent has yet been found. The therapeutic potentialities of sulfanilamide and its derivatives have yet to be fully explored. This case details an instance which suggests that sulfanilamide compounds may be bactericidal to blood-borne tularemic organisms. Laboratory studies and further clinical investigation are necessary to determine the efficacy of sulfanilamide and its derivatives in tularemia.

Tularemic septicemia may occur quite late in the course of the disease, and thereby present itself as a complication. An example of such an occurrence is detailed here.

The primary lesion of tularemia is not necessarily an ulcer. An unusual primary lesion, consisting of a cellulitis of two terminal phalanges of the hand, is described.

An unusual skin eruption, concurrent with the late septicemia, is described.

The use of sulfanilamide compounds, followed by rapid recovery, in an unusual, severe, and protracted case of tularemic septicemia, is reported.

REFERENCES

- 1 CURTIS, W. L. Sulfanilamide in the treatment of tularemia, Jr. Am. Med. Assoc., 1939, cxiii, 294.
- 2 FRANCIS, EDWARD. In Brennemann, Practice of pediatrics, chapter 29.
- 3 HITCH, J. M., and SMITH, D. C. Cutaneous manifestations of tularemia, Arch. Dermat. and Syph., 1938, xxxviii, 859-876.
- 4 PERRET, J. M. Study of 69 cases of tularemia, New Orleans Med. and Surg. Jr., 1936, lxxxviii, 694-702.
- 5 WOOLEY, P. G. The lesions in experimental infection with *B. tularensis*, Jr. Infect. Dis., 1915, xvii, 510-513.
- 6 FRANCIS, E. Tularemia, microscopic changes of lesions in man, Arch. Path. and Lab. Med., 1927, iii, 577.
- 7 GOODPASTURE, E. W., and HOUSE, S. J. Pathological anatomy of tularemia in man, Am. Jr. Path., 1928, iv, 213-226.
- 8 GUNDRY, L. P., and WARNER, C. J. Fatal tularemia: review of autopsied cases, ANN. INT. MED., 1934, vii, 837-852.

UNILATERAL RENAL TUBERCULOSIS ASSOCIATED WITH HYPERTENSION¹

By G GILL RICHARDS, M D , F A C P , *Salt Lake City, Utah*

BECAUSE Goldblatt¹ could, by removing the ischemic kidney in his experimental hypertensive dogs, cause a fall of blood pressure to normal, the possible clinical application of his results to cases of essential hypertension in man aroused considerable interest, particularly among internists and urologists. The following report deals with a case of unilateral renal tuberculosis with hypertension and the satisfactory result which has continued for 11 months after nephrectomy.

CASE REPORT

L. P., a married white male, aged 37 years, was admitted to the Latter-Day Saints Hospital on January 10, 1940, complaining of occipital headaches of extreme degree, fatigue, shortness of breath upon exertion, insomnia, extreme irritability and pounding of his heart.

Past History At 13 years of age this patient had mumps accompanied by orchitis of the right testicle, resulting in its atrophy to one-third its normal size. At the age of 20 years he had what was diagnosed as typhoid fever. During this illness he had a leukocytosis ranging from 9,600 to 12,000, which is unusual for typhoid. He also developed a cough and an effusion in his left pleural cavity. This fluid did not reveal any organisms upon culture, and no tubercle bacilli were found in the sputum. The Widal reaction was positive, but there had been prior inoculations against typhoid fever.

He was married at 22 years and his wife had one child in the first year and none since. At 23 years of age (in 1925) he injured his left testicle. This resulted in a suppurating orchitis which drained spontaneously two months after the injury and continued for one year. In 1928 a diagnosis of tuberculous epididymitis on the left side was made, for which he refused operation.

Urinalysis at this time showed no albumin but an occasional red blood cell. His blood pressure was systolic 126 and diastolic 80 mm Hg.

In 1930 the patient began to have attacks of hiccoughs which have since recurred intermittently. During the last five years he has had to get up once at night to void. In 1937 he began to have occasional headaches. His blood pressure was reported normal at that time but he does not know the exact readings.

Present Illness During the latter part of 1938 some shortness of breath was noted upon exertion. In February 1939 he began to be nervous and irritable. The headaches became more frequent and severe. An examination in May 1939 revealed a systolic blood pressure of 180 mm Hg. He weighed 189 pounds and was advised to lose weight.

In July 1939, while at an altitude of 11,000 feet, he became very short of breath, weak and faint. During that summer and fall insomnia developed, with increasing nervousness and irritability. He also complained of pains in his back in the region of his left kidney, and that his heart pounded very hard.

On January 10, 1940 he was admitted to the hospital, two days after a peculiar nervous attack which greatly alarmed his doctor and family. It consisted of severe headache associated with generalized numbness and twitching. The essential physical findings were: Weight 177 pounds, 12 pounds under his usual weight. Temperature 98.4° F, pulse 82, blood pressure systolic 210, diastolic 150. He was extremely

* Received for publication December 27, 1940

nervous, apprehensive and irritable, the reflexes were exaggerated but no abnormal ones were present. The heart showed accentuation of the second aortic sound with little or no enlargement either on percussion or on a seven foot roentgen-ray film. His blood vessels seemed neither tortuous nor obviously thickened. There was no palpable mass in the abdomen but there was some tenderness to hard percussion over his left kidney. There was a hard nodular mass in his left epididymis.

Laboratory findings. Blood hemoglobin 87 per cent, red blood cells 5,150,000, white blood cells 10,750, the differential count being 81 per cent polymorphonuclear neutrophils, 16 per cent lymphocytes, 2 per cent large mononuclears, and 1 per cent



FIG 1 Intravenous pyelogram showing normal right kidney and nonfunctioning left kidney

eosinophiles. The urea nitrogen was 21.4 mg per cent, the creatinine 1.08 mg per cent. The Wassermann reaction was negative. Urine, specific gravity 1.012, alkaline, with a trace of albumin and an occasional pus cell. The urine concentration test ranged from 1.009 to 1.022. The phenolsulfonphthalein output was normal. Spinal puncture revealed normal pressure, normal jugular response and normal fluid. Intravenous pyelograms on two occasions showed a normal right kidney and ureter, but no shadow at all on the left side. Cystoscopy showed a normal ureter and kidney with normal function on the right side, but merely a small dimple at the site of the left ureteral orifice from which no urine or dye appeared.

The fundi showed a slight tortuosity of the vessels with mild arterio-venous compression, no hemorrhages, exudates, or edema of the disc.

He had a labile type of hypertension and under sedation with sodium amytal his blood pressure dropped as low as systolic 150, diastolic 100. The headaches were relieved with the drop in pressure.

On the fifteenth day of his hospital stay Dr. Ralph Richards removed the left kidney. The kidney was less than one-half its normal size, weighing 73 gm. The pelvis was distended with a thick caseous material which also filled the ureter. There was a considerable amount of fairly healthy looking kidney cortex to which the capsule was only slightly adherent.

Microscopically it showed hyalinization of all the glomeruli and marked increase in interstitial tissue which constricted the tubules. There were giant cells in some areas. The vessels of the pedicle and all the small arterioles showed marked intimal proliferation with narrowing of the lumen. The pathological diagnosis was tuberculosis of the kidney with advanced caseation, and arteriosclerosis.

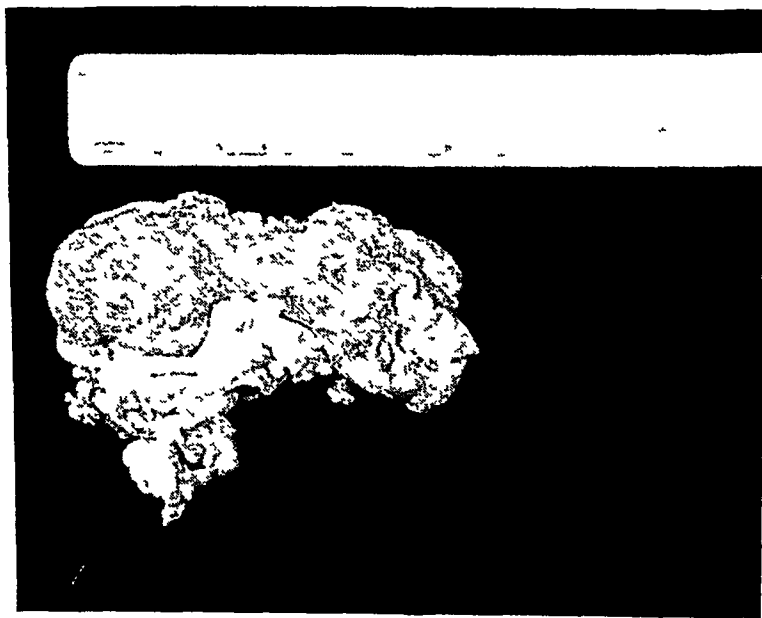


FIG 2 Gross specimen of left kidney weighing 73 gm

At the beginning of the operation the pressure was systolic 230, diastolic 140, and the pulse 92. After the kidney pedicle was clamped, the pressure began to fall. One hour after completion of the operation it was systolic 102, diastolic 80. It dropped as low as systolic 80 and 60 diastolic after operation. A transfusion of 500 c.c. of blood was given, and the blood pressure rose to systolic 120, diastolic 80. During the next 15 days it ranged from systolic 154 to 176 and diastolic 88 to 108, and seemed to depend upon the amount of pain present.

Fifteen days after the nephrectomy his left epididymis was removed. At the time of discharge from the hospital, the blood pressure was systolic 130, diastolic 74, and the patient was symptom free.

During the next 11 months the pressure has ranged from systolic 118 to 128 and diastolic 78 to 86. He is now back at work and apparently cured of all his complaints except some backache.

Among the cases reported since Goldblatt's communication are Butler's² two cases in children with hypertension and unilateral pyelonephritis in whom nephrectomy was followed by return to normal blood pressure. One case, in a child of 10 years, was reported by Barney and Suby,³ and three were reported by

Ciabtice⁴, Leadbetter and Buland⁵ reported the case of a negro boy, age five and one half years, who was known to have had hypertension for three years, with complete relief after removal of an ectopic kidney in which the main artery was partially occluded. Boyd and Lewis⁶ reported similar results after removal of a kidney containing multiple infarcts. Barker and Walters⁷ of the Mayo Clinic reported five cases of unilateral pyelonephritis associated with hypertension in patients ranging in age from 7 to 52 years. After removal of the kidney in all these cases the blood pressure returned to normal. Their report covered a post-operative period of from 6 to 29 months. The mean blood pressure before operation varied from systolic 178 to 210 and diastolic 118 to 166. All kidneys removed weighed 75 gm or less (less than half the normal size) and all the kidneys showed a considerable thickening of the arterial walls in the areas of

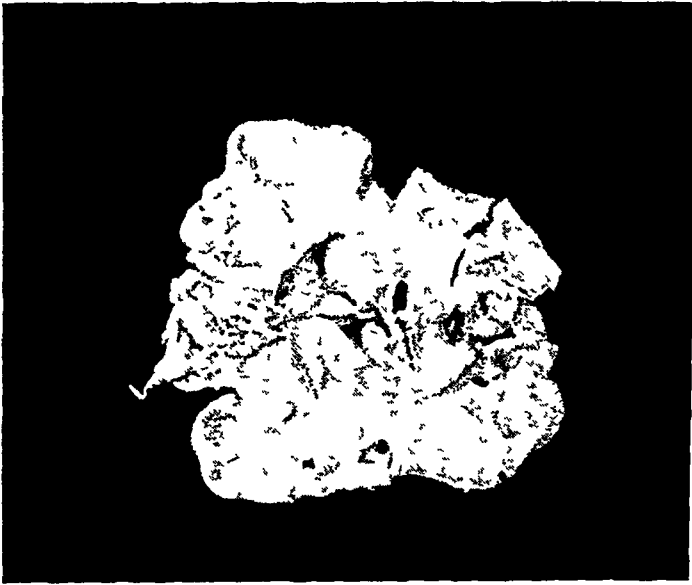


FIG 3 Cut specimen of same kidney

definite renal sclerosis. None of the cases had evidence of advanced generalized arterial damage.

A very instructive case was reported by Fitz⁸. A man 40 years of age with a history of pain in the right side of his abdomen for four years, for which appendectomy had given no relief, developed headaches, persistent hypertension, acute hemorrhagic nephritis following acute tonsillitis, and later hemorrhagic retinitis. He had had a bilateral sympathectomy with no relief in 1937. One year later, because the right kidney seemed smaller in the urogram than when examined the year before, and in spite of an apparent normal kidney function, his right kidney was removed. It weighed only 30 gm. His pressure returned to normal, all his symptoms disappeared, and he has remained well since.

Undoubtedly the cases in which the so-called Goldblatt kidney is the cause of hypertension in man are comparatively rare. Up to date, probably not more than 20 have been reported. So far as I have reviewed the literature, this is the only case yet reported of relief of hypertension associated with removal of a tuberculous kidney.

The varied pathological conditions found in the kidneys removed on account of hypertension, as listed in the accompanying bibliography, and the results following nephrectomy in carefully studied and selected cases, would seem to be sufficient justification for special urological study in most all cases of so-called essential hypertension, the majority of which will reveal no unilateral kidney disease

However, the drop in blood pressure and the relief of symptoms which may follow the removal of a unilateral hydronephrotic or pyonephrotic kidney associated with hypertension, is a result to be sought

We have studied our hypertensives more carefully during the past year and have discovered two patients who presented no symptoms referable to their hydronephrotic kidneys

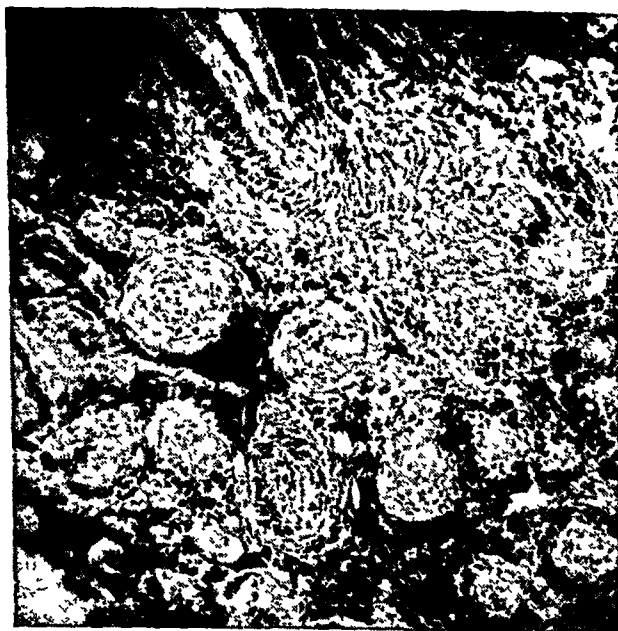


FIG 4 Microphotograph of kidney showing the marked blood vessel changes

It is too soon to venture an opinion as to the length of time one might expect this relief of the hypertension to continue following unilateral nephrectomy in these cases. Many investigators think it depends upon the condition of the remaining kidney

BIBLIOGRAPHY

- 1 GOLDBLATT, HARRY Studies on experimental hypertension due to renal ischemia, *ANN INT MED*, 1937, xi, 69-103
- 2 BUTLER, A M Chronic pyelonephritis and arterial hypertension, *Jr Clin Invest*, 1937, xvi, 889-897
- 3 BARNEY, J D, and SUBY, H I Unilateral renal disease with arterial hypertension, *New England Jr Med*, 1939, ccxx, 744-746
- 4 CRABTREE, E G Hypertension in destructive infected unilateral lesions of the kidney, *Trans Am Assoc Genito-Urin Surgeons*, 1938, xxxi, 299-319
- 5 LEADBETTER, W F, and BURLAND, C E Hypertension in unilateral renal disease, *Jr Urol*, 1938, xxxix, 611-626
- 6 BOYD, C H, and LEWIS, L G Nephrectomy for arterial hypertension, *Jr Urol*, 1938, xxxix, 627-635
- 7 BARKER, NELSON W, and WATERS, WALTER Hypertension and chronic pyelonephritis results of nephrectomy, *Jr Am Med Assoc*, 1940, cxv, 912-916
- 8 FITZ, REGINALD Hypertension, *Mississippi Doctor*, 1940, vii, 531-541

EDITORIAL

THE PATHWAY OF INFECTION IN POLIOMYELITIS

THE problem of the pathogenesis of poliomyelitis—its portal of entry, the manner of the distribution of the virus in the body tissues and the route by which it is disseminated—has not yet been satisfactorily solved, in spite of much intensive investigation

The study of the disease is beset with many practical difficulties. One of the greatest of these is the fact that the monkey is the only animal susceptible to the filtrable virus which causes the disease, and successful inoculation of these animals is the only method of demonstrating its presence. Even monkeys appear to differ in susceptibility, and individual animals may escape infection or present subclinical or abortive attacks without the typical paralysis. Relatively large doses appear to be required to infect the monkey, as compared with many other filtrable viruses, and this animal can not be regarded as a sensitive indicator of the virus. It is, therefore, necessary to use several animals in important experiments.

Although by special methods mice can be infected with certain passage strains, they are not susceptible to inoculations of human material, and failure to produce an encephalitis by intracerebral inoculation of virus into mice and other common laboratory animals is one criterion for the identification of the virus.

Epidemiological and clinical studies of human cases have shown great individual variation in susceptibility. Evidently many are naturally refractory or become so as the result of a subclinical infection. Even among those clinically ill it is probable that there are from four to six abortive cases to each one showing the typical paralytic lesions. There is as yet no practicable means of identifying such cases positively, and the diagnosis is rarely even suspected except during an epidemic. Although occasional instances have been reported in which direct contact infection has occurred, this is relatively rare. In most cases infection must be acquired from abortive cases or carriers. Such observations, however, have shed little light on the problems under discussion.

The virus of poliomyelitis has a special predilection for the nervous system, in which the characteristic lesions are found. It is generally believed that the virus reaches the nervous system by centripetal passage through the nerve trunks. Nonmedullated fibers appear to be especially vulnerable to attack. The possibility of transmission by lymph and blood stream has also been claimed, particularly by Kling and Levaditi, but their experiments are open to criticism.

After reaching the central nervous system the virus becomes widely disseminated, presumably by direct extension, throughout the motor areas in the cortex, medulla and entire spinal cord. This has been shown by inoculation of tissue from these regions into monkeys, and also by the occurrence here of the typical histological lesions, consisting of necrosis and disappearance of motor cells, and round cell infiltrations about the vessels and in the gray matter. It has also been shown that in monkeys there is a centrifugal spread of virus to the periphery along the nerve trunks, such as occurs in rabies.

Flexner has long maintained that the nasopharynx constitutes the portal of entry, and probably also of exit of the virus. This view is based in part on the fact that the virus has been demonstrated repeatedly (although not regularly) in washings from the nasopharynx, and in extracts of the mucosa of that region in human cases. Monkeys can easily be infected by intranasal inoculations of virus, and the infecting dose is smaller than when given by injection in other regions. The virus is believed to enter through the olfactory mucous membrane and to reach the brain by passage through the olfactory tracts. This view is supported by the presence of typical histological lesions in the olfactory bulbs of monkeys so inoculated, although according to Sabin and Olitsky they are not present in animals infected by other routes. It has been generally assumed that this is also the mode of infection in man, and that the virus is disseminated in the nasal secretions, by droplet infection.

Other investigators, however, have held that the portal of entry is to be found in the gastrointestinal tract. This view has recently received support from Levaditi and Kling¹ on the basis of feeding experiments. By introducing virus through a stomach tube as well as by feeding materials contaminated with virus, they succeeded in infecting several animals. They also obtained infection by injecting virus, by needle, directly into the lumen of the ileum. In two cases they found virus in the mesenteric glands, and they think it may reach the brain through the circulation.

Flexner² and his associates, however, repeated these experiments with essentially negative results. The occasional successful case they attributed to contamination of the nasal mucosa with the virus, or to introduction of virus into the tissues of the intestinal wall by the needle.

There is now conclusive proof that the virus occurs in the feces, sometimes in considerable concentration, and that it may remain viable there for substantial periods of time. Thus, Paul, Trask and their associates³ demonstrated virus in 10 of 56 specimens examined, obtained from cases of the

¹ LEVADITI, C., KLING, C., and HORNUS, G. Transmission expérimentale de la poliomyélite par la voie digestive, *Compt. rend. Soc. de biol.*, 1933, cxii, 43-45.

² FLEXNER, S. Respiratory versus gastrointestinal infection in poliomyelitis, *Jr. Exper. Med.*, 1936, lxiii, 209-226.

³ TRASK, J. D., PAUL, J. R., and VIGNEC, A. J. I. Poliomyelitic virus in human stools, *Jr. Exper. Med.*, 1940, lxxi, 751-764.

disease in several different epidemics. Positive results were obtained with two specimens which had been in the mail (from England) for two weeks in summer weather before they were examined. They⁴ were also able to demonstrate virus in several instances in sewage taken from mains in the vicinity of isolation hospitals during epidemics of the disease. In one specimen the virus had survived in sewage which had flowed for at least one sixteenth of a mile. If the virus were uniformly distributed throughout the sewage there would have been 18,000 infective doses per minute discharged at that point.

Thus far, however, there is no direct proof that infection is conveyed in this manner. The virus might be swallowed after being eliminated in the nasopharynx, and its presence in the feces merely an incidental phenomenon.

Recently Sabin and Ward⁵ have tried to get additional evidence bearing on this problem by a study of the distribution of the virus in human tissues. They point out that although there are many reports of the isolation of virus from various human tissues, there have been no comprehensive studies of many tissues from the same individual. Accordingly they inoculated monkeys with 22 different tissues from each of nine fatal cases of human poliomyelitis. In two cases they failed to demonstrate any virus, but in the other seven cases they recovered it from two or more sites.

In general their results do not support the view that the virus enters through the olfactory pathway. Although usually found in the motor areas of the brain and cord, in no case was it found in the olfactory bulbs, and these did not show the histological lesions characteristic of the bulbs of monkeys infected by the nasal route. In no case was virus demonstrated in the nasal mucosa, although it was found in the mucosa of the pharynx in four cases. It was found in three cases in the washed wall of the ileum, although not demonstrated in the contents of the ileum in two of them. It was found in the contents of the ileum in two cases, and in those of the descending colon in all six cases in which material was available for examination.

The failure to demonstrate virus in the salivary glands, suprarenal glands, lymph nodes or sympathetic ganglia (with one exception) led them also to question the theory of a centrifugal distribution of virus from the central nervous system through the nerve trunks. They concluded that their findings point to the gastrointestinal tract as the portal of entry and site of primary localization of the virus.

The evidence presented by these investigators is manifestly indirect, but it raises serious doubt as to whether the virus entered through the olfactory

⁴ PAUL, J. R., TRASK, J. D., and GARD, S. II. Poliomyelitic virus in urban sewage, Jr. *Exper. Med.*, 1940, **XXI**, 765-778.

⁵ SABIN, A. B., and WARD, R. The natural history of human poliomyelitis. I. Distribution of virus in nervous and non-nervous tissues, Jr. *Exper. Med.*, 1941, **XXXII**, 771-794.

pathway in these cases. It is impossible to reconcile these findings with the work and views of Flexner except by assuming either that these cases were all highly exceptional, or that man differs radically from the monkey in his response to the virus. Further investigations are obviously needed to decide the question. Until this is accomplished, the frequent presence of the virus in the feces is a fact which can not safely be disregarded.

P W C

REVIEWS

Arthritis and Allied Conditions By BERNARD I COMROE, A B, M D, F A C P
Second Edition 878 pages, 24 × 15.5 cm Lea and Febiger, Philadelphia
1941 Price, \$9.00

This book is really the complete story of arthritis as known today. It begins with the occurrence of the disease in the prehistoric period of man and beast and ends with the latest information on the sulfonamides. The 50 chapters and 2644 bibliographic references give ample evidence of the wide extent of the author's review of the literature and his tremendous amount of work. The illustrations are excellent and indeed speak for themselves. In addition to the chapters on etiology and pathology and general therapy a large portion of the book is devoted to the special methods of treatment, such as fever therapy, massage and kinds of shoes to be worn. The author's therapeutic recommendations show conservatism and caution, for example, while his statistics on gold therapy are quite encouraging, yet every patient is asked to sign a statement, witnessed by two additional persons, 'assuming the responsibility for complications which might arise from this form of therapy.' In the experience of this reviewer such a procedure is urgently recommended.

The related conditions cover a wide field such as painful feet, backache, internal derangement of the knee joints, tumors of joints and tendon sheaths and the sulfonamides. The text is well written, the style is easy to read in spite of the many assembled details. An attractive feature for the busy general practitioner is the inclusion of summaries presented in box form outlines, enabling him to obtain quickly most of the information he requires.

The book is based on the author's personal experiences but it contains a comprehensive review of the literature. It can be highly recommended as an excellent and up to date reference book which will have an especial appeal to the internist and orthopedist.

L A M K

Modern Diabetic Care By HERBERT POLLACK, A B, Ph D, M D 216 pages, 21 × 14 cm Harcourt, Brace and Co, New York 1940 Price, \$2.00

This is a complete manual designed for the diabetic patient. Throughout the book, of about 200 pages, technical language has been avoided but where used has been well explained in lay terms. The diabetic diet is discussed in a simple and complete manner. "The highly important matter of feeding the diabetic is not one that requires careful minute specialization. Rather, it is only a problem of making slight alterations and simple adjustments in a well balanced, normal diet." Probably if this statement were really understood and practiced, diabetics as a group would be receiving far better treatment today.

The chapter on protamine zinc insulin is most valuable to both patient and physician. The rather brief discussion of the problems Shall Diabetics Marry? Are Diabetics Safe Automobile Drivers? For What Trade May Young Diabetics Be Trained? are most valuable. There are the sections dealing with food equivalents and substitutions, recipes, and food combinations usually found in books of this type. The index is complete and workable.

There are already many diabetic manuals in print but the reviewer feels that this small volume occupies an unusual position. Throughout the many interesting chapters the author has kept in mind that the patient is just a busy layman, not trained in medicine, but interested in finding out briefly but thoroughly how to care for his diabetes. The book is most heartily recommended.

H P

The Endocrine Function of Iodine By WILLIAM THOMAS SALTER, Assistant Professor of Medicine, Harvard Medical School 351 pages, 24 × 16 cm Harvard University Press, Cambridge, Massachusetts 1940 Price, \$3 50

This volume is one of the Harvard University Monographs in Medicine and Public Health. The title gives only a hint of the complete review of the subject presented by the author. A survey of some headings in the table of contents may suggest the comprehensive character of the work.

The introductory chapter discusses briefly iodine balance and endocrine balance. Other chapters take up iodine stores in body tissues, iodine compounds of biological importance, circulating iodine in air, lymph, cerebrospinal fluid, milk, sweat, saliva and blood. In the chapter on circulating iodine, the discussion of blood iodine is most complete and detailed.

Later chapters are concerned with thyroid activity, endocrine balance, iodine and the "pituitary-ovarian axis," neurological influence of the thyroid hormone, and studies with radioactive iodine. The final chapter is probably the most interesting to the practicing physician, and introduces some clinical problems. Cases studied at the Boston City Hospital are reported, and the value of blood iodine determinations in the differential diagnosis of thyroid disease is discussed.

The book closes with a 20 page appendix for laboratory workers, describing methods for the determination of the blood iodine content, and separation of protein and non-protein fractions.

T N C

Landmarks in Medicine Laity Lectures of the New York Academy of Medicine Introduction by JAMES ALEXANDER MILLER, M D 347 pages, 20 × 13.5 cm D Appleton-Century Company, New York 1939 Price, \$2 00

The New York Academy of Medicine, through its annual series of "Laity Lectures," has done much to stimulate interest in medical history and thus foster a better mutual understanding between the medical profession and the laity. "Landmarks in Medicine" is the third publication in this series. In the introduction it is stated, "The New York Academy of Medicine has long recognized as an obligation the interpretation of the progress of medical knowledge to the public."

The eminent contributors to this volume and their subjects are as follows: "From Barber-Surgeons to Surgeons" by Francis R. Packard, M D, "The Meaning of Medical Research" by Alfred E. Cohn, M D, "Dr. Watson and Mr. Sherlock Holmes" by Harrison Stanford Martland, M D, "Medicine in the Middle Ages" by James J. Walsh, M D, "The Search for Longevity" by Raymond Pearl, M D, "Medicine and the Progress of Civilization," by Reginald Burbank, M D, and "X-Ray Within the Memory of Man," by Lewis Gregory Cole, M D.

While this little book may be read with real interest by the layman for whom it was intended, it will also be warmly appreciated by any member of the medical profession.

J E S

The Early Diagnosis of the Acute Abdomen By ZACHARY COPE, B A, M D, M S Lond, F R C S Eng 257 pages, 22.5 × 14.5 cm Oxford University Press, New York 1940 Price, \$3 75

An excellent compendium or roll-call of the conditions which are commonly responsible for the acute abdomen, stressing the history, methods of examination and differential points for early diagnosis.

This illustrated book, written in large print, limited to 244 pages, should prove of particular value, first to students, in giving them an organized and concise picture of

such a vast subject, and second to practitioners, in giving a review of diseases so consistently and commonly responsible for abdominal distress

The author stresses the value of history taking, examination, anatomy and physiology in the interpretation of symptoms in making a diagnosis. Laboratory work, though mentioned, is not accentuated, which may be considered justifiable since so many surgical patients are first seen in homes where laboratory facilities are nil and the doctor must rely on other criteria in reaching a diagnosis.

Common surgical conditions are reiterated. Rarer diseases are mentioned in differential diagnostic tables, though no mention was made of nonspecific terminal ileitis, mesenteric adenitis, Meckel's diverticulitis, or rupture of the corpus luteum, conditions which in late years have gained some notice.

As evidenced by the many editions of this publication, a summary of so large a subject is still well received.

H C H

COLLEGE NEWS NOTES

GIFTS TO THE COLLEGE LIBRARY

Acknowledgment is made of the receipt of the following reprints by members of the College

Dr Robert H Bayley, F A C P, New Orleans, La —8 reprints,
Dr Victor W Bergstrom, F A C P, Binghamton, N Y —1 reprint,
Dr Edward G Billings, F A C P, Denver, Colo —2 reprints,
Dr Edward W Bixby, F A C P, Wilkes-Barre, Pa —1 reprint,
Dr Hildahl I Burtness, F A C P, Santa Barbara, Calif —2 reprints,
Dr Verne S Caviness, F A C P, Raleigh, N C —2 reprints,
Dr Richard E Ching, F A C P, Memphis, Tenn —1 reprint,
Dr William P Garver (Associate), Cleveland, Ohio —2 reprints,
Dr Edward S King, F A C P, Winston-Salem, N C —2 reprints,
Dr Phillip T Knies, F A C P, Columbus, Ohio —6 reprints,
Dr Charles J Koerth (Associate), San Antonio, Tex —2 reprints,
Dr Charles A LaMont, F A C P, Canton, Ohio —2 reprints,
Dr Rudolf Leiser, F A C P, Eloise, Mich —1 reprint,
Dr William H Ordway, F A C P, Mount McGregor, N Y —2 reprints,
Dr Dale P Osborn, F A C P, Cincinnati, Ohio —1 reprint,
Capt John R Poppen, F A C P, (MC), U S Navy —1 reprint,
Dr Ellen C Potter, F A C P, Trenton, N J —1 reprint,
Dr Harry Plummer Ross (Associate), Richmond, Ind —1 reprint,
Dr Ernest G Scott, F A C P, Lynchburg, Va —1 reprint,
Dr Bernard Seligman (Associate), Brooklyn, N Y —2 reprints,
Dr Hugh Smith, F A C P, Greenville, S C —1 reprint,
Dr Edward R Snader, Jr, F A C P, Philadelphia, Pa —18 reprints,
Dr Harry P Thomas (Associate), Rusk, Tex —2 reprints,
Dr Henry J Tumen (Associate), Philadelphia, Pa —1 reprint,
Dr Edward L Turner, F A C P, Nashville, Tenn —4 reprints,
Dr F Howard Westcott, F A C P, New York, N Y —1 reprint,
Dr Arthur T Wyatt, F A C P, Lillington, N C —1 reprint

A C P BECOMES MEMBER, DIVISION OF MEDICAL SCIENCES OF THE NATIONAL RESEARCH COUNCIL

The American College of Physicians has been appointed by the unanimous action of the Executive Board of the National Research Council a member society in the Division of Medical Sciences of that body Dr O H Perry Pepper, F A C P, Philadelphia, has been appointed the College representative in the Division Dr Pepper is also Chairman of the Committee on Medicine of the Division of Medical Sciences of the Council

The National Research Council was established in 1916 by the National Academy of Sciences under its congressional charter and supported by the cooperation of national scientific and technical societies of the United States The Council is a representative organization of the scientific men of America Its members include not only scientific and technical men, but also business men interested in engineering and industry The membership of the Council is composed largely of appointed representatives of the scientific and technical societies and includes representatives also of certain other research organizations representatives of Government scien-

the bureaus, and a limited number of members at large. The Council actually was organized at the request of President Woodrow Wilson as a measure of national preparedness. The work accomplished by the Council in organizing research and in securing cooperation of military and civilian agencies in the solution of military problems demonstrates its capacity for larger service. The Council is carried on by a small group of officers and an Executive Board, with an Administrative Committee which acts for the Board between its annual meetings. The Council is composed of nine major divisions arranged in two groups. One group comprises seven divisions of science and technology, the other group comprises two divisions of general relations, representing foreign relations and educational relations. The Division of Medical Sciences is one of the seven divisions of science and technology, and Dr Lewis H. Weed, Professor of Anatomy and Director of the School of Medicine of Johns Hopkins University, Baltimore, is the Chairman. The Division has more than a score of committees and sub-committees, and it cooperates with other Divisions of the Council in connecting with the activities of some of their committees. A large proportion of its committee chairmen and members are Fellows of the American College of Physicians.

The newly-organized American Diabetes Association held its First Annual Session at Cleveland, June 1, 1941. Its initial officers were

Elliott P. Joslin, M.D., F.A.C.P., Boston, Honorary President
 Cecil Striker, M.D., F.A.C.P., Cincinnati, President
 Herman O. Mosenthal, M.D., F.A.C.P., New York City, First Vice-President
 Joseph T. Beardwood, Jr., M.D., F.A.C.P., Philadelphia, Second Vice-President
 Samuel S. Altshuler, M.D., F.A.C.P., Detroit, Secretary
 William Muhlberg, M.D., Cincinnati, Treasurer

Over 350 physicians attended the meeting, and it has been decided that the next meeting will be held on the day preceding the opening of the American Medical Association meeting at Atlantic City, June, 1942.

Current officers include

Herman O. Mosenthal, M.D., F.A.C.P., President
 Joseph T. Beardwood, Jr., M.D., F.A.C.P., First Vice-President
 Joseph Barach, M.D., F.A.C.P., Pittsburgh, Second Vice-President
 Cecil Striker, M.D., F.A.C.P., Secretary
 William Muhlberg, M.D., Treasurer

Among members of its Board of Trustees are

Dr. James E. Paullin, F.A.C.P., Atlanta, Dr. W. D. Sansum, F.A.C.P., Santa Barbara, Dr. Edward S. Dillon, F.A.C.P., Philadelphia, Dr. James Ralph Scott, F.A.C.P., New York City, Dr. H. Clare Shepardson, F.A.C.P., San Francisco, Dr. L. H. Newburgh, F.A.C.P., Ann Arbor, Dr. Russell M. Wilder, F.A.C.P., Rochester, Minn., Dr. Seale Harris, F.A.C.P., Birmingham, Dr. Henry John, F.A.C.P., Cleveland, Dr. Edward H. Mason, F.A.C.P., Montreal, Dr. Howard F. Root, F.A.C.P., Boston.

The Association is engaged in appointing committees, to study the problem of the publication of a journal, to work with the American Dietetic Association on the question of foods and diets, to cooperate with the Federal Food and Drug Administration on fraudulent diabetic cures, to study the problem of assisting in the foundation of local diabetes associations.

Dr Clifford W Mack, F A C P , Livermore, Calif , was recently elected an Administrative Member at large of the California Physicians Service by its Board of Trustees

Dr William A Groat, F A C P , Syracuse, N Y , has been elected Chairman of the Board of Trustees of the Medical Society of the State of New York for the 1941-42 term

Dr. Jacob Casson Geiger, F A C P , Director of Public Health of the City and County of San Francisco, recently received the Officer's Cross of the Order of the Southern Cross of Brazil This decoration was conferred by President Vargas of Brazil with the following citation "For eminency in preventive medicine and public health"

On July 10, 1941, the 11th Councilor District of the Medical Society of the State of Pennsylvania held its annual meeting in Johnstown "The Management of Allergic Conditions of the Respiratory Tract" and "Silicosis" were among the topics discussed Dr Francis F Borzell, Philadelphia, President of the Medical Society of the State of Pennsylvania spoke on "Medical Preparedness" Dr Laurie D Sargent, F A C P , Washington, Trustee and Councilor, presided

Dr Alexander H Stewart, F A C P , Harrisburg, Pa , was recently appointed Acting Director of the Pennsylvania State Department of Health, succeeding Dr John Shaw, who died suddenly June 24, 1941

Dr Allen H Bunce, F A C P , Atlanta has been installed as President of the Medical Association of Georgia

Dr Frank N Wilson, F A C P , Ann Arbor, Mich , was recently elected an honorary member of the Cardiac Society of Great Britain and Ireland

Dr Francis D Murphy, F A C P , Milwaukee, Wis , spoke on "Clinical Application of the Sulfonamide Group of Drugs" at a meeting of the Upper Peninsula Medical Association in Ironwood, Mich , July 17-18, 1941

Dr Thomas K Lewis, F A C P , Camden, was installed as President of the Medical Society of New Jersey at its annual meeting in Atlantic City, May 20-22, 1941 Dr Ralph K Hollinshed, F A C P , Westville, was elected a Vice-President of the Society

At the recent annual meeting of the State Medical Association of Texas held in Fort Worth, Dr Neil D Buie, F A C P , Marlin, was installed as President Dr

Caleb O Terrell, F A C P , Fort Worth, was elected one of the Vice-Presidents of the Association

Dr Maurice C Pincoffs, F A C P , Baltimore, Md , was one of the lecturers at the 25th Anniversary Course of Lectures and Clinics presented by the University of Washington July 14-18, 1941

Dr Bruce H Douglas, F A C P , Detroit, Mich , was elected President of the National Tuberculosis Association at its recent annual meeting in San Antonio, Tex , and Dr J Burns Amberson, Jr , F A C P , New York, N Y , was named President-Elect Dr Henry F Carman, F A C P , Dallas, Tex , was elected a Vice-President of the Association

Dr David C Wilson, F A C P , Charlottesville, Va , was elected one of the Vice-Presidents of the American branch of the International League Against Epilepsy at its annual meeting in Richmond, Va , May 5, 1941

Dr Arthur M Master, F A C P , and Dr Frederick R Bailey, F A C P , have been promoted to Assistant Clinical Professors of Medicine at Columbia University College of Physicians and Surgeons, New York, N Y

Among the speakers at a joint meeting of the 6th and 8th Councilor Districts of the State Medical Society of Wisconsin held in Appleton, May 27, 1941, were

Dr William S Middleton, F A C P , Madison, Wis —“Bronchiogenic Carcinoma ”,

Dr Walter C Alvarez, F A C P , Rochester, Minn —“Puzzling Types of Indigestion ” and “Food Allergy ”

Dr John A Toomey, F A C P , Cleveland, Ohio, spoke on “Pathogenesis of Poliomyelitis ” at the annual meeting of the Iowa and Illinois Central District Medical Association, June 26, 1941, in Davenport, Iowa

Dr John T Murphy, F A C P , Toledo, Ohio, delivered the 1941 Hickey Memorial Lecture at a joint meeting of the Wayne County Medical Society and the Detroit Roentgen Ray and Radium Society, April 7, 1941 Dr Murphy spoke on “The Use of X-Ray in the Treatment of Carcinoma of the Skin ”

Dr David B Jewett, F A C P , Rochester, N Y was awarded the Albert D Kaiser Medal “for distinguished service to the medical profession ” at the annual meeting of the Rochester Academy of Medicine, May 6, 1941 Dr Jewett received this award for his efforts in building up the Academy's library

On May 26, 1941, Dr. Graham Asher, F A C P, Kansas City, Mo., addressed the Tulsa (Okla.) County Medical Society on "Chemical, Nutritional and Clinical Factors Influencing the Administration of Digitalis"

Dr. John S. Hibben (Associate), Pasadena, Calif., spoke on "Clinical Evaluation of Various Heart Energies" at the 9th Annual Seminar of the Western Section of the American Congress of Physical Therapy held in Los Angeles, Calif., June 22, 1941

Dr. Russell L. Haden, F A C P, Cleveland, Ohio, has been elected Vice President of the American Society of Clinical Pathologists

Dr. Benjamin Goldberg, F A C P, Chicago, Ill., was installed as President of the American College of Chest Physicians at its annual meeting in Cleveland, Ohio, May 31-June 2, 1941. Dr. J. Winthrop Peabody, F A C P, Washington, D. C., was named President-Elect of this society and Dr. Jay Arthur Myers, F A C P, Minneapolis, Minn., a Vice-President

Dr. John T. Murphy, F A C P, Toledo, Ohio, was one of the speakers at the 7th Midsummer Radiologic Conference of the Denver Radiological Club, which was held July 31-August 2, 1941. Dr. Murphy spoke on "Carcinoma of the Skin"

Dr. Roy L. Leak, F A C P, Middletown, has been chosen President-Elect of the Connecticut State Medical Society

Dr. Henry N. Tihen, F A C P, Wichita, was named President-Elect of the Kansas Medical Society at its annual meeting in Topeka in May. Dr. John M. Porter (Associate), Concordia, was reelected Secretary of the Society

Dr. Herbert Z. Giffin, F A C P, Rochester, has been elected President of the Minnesota State Medical Association. Dr. Benjamin B. Souster, F A C P, St. Paul, was reelected Secretary of the Association

On May 29, 1941, Dr. Joseph H. Barach, F A C P, Pittsburgh, Pa., addressed the Glens Falls (N. Y.) Academy of Medicine on "Present Day Treatment of Diabetes and Its Complications," and spoke on "Inheritance and Tumors" at the Albany Medical College, Albany, N. Y.

The Board of Estimate and City Council of the City of New York have authorized the establishment, under the New York City Department of Health, of the Public Health Research Institute of New York, Inc. This Institute is to be used exclusively for scientific research "essential for the protection and the improvement of the health, safety and welfare of the people of New York City." This Institute will be directed by a lay board to supervise the business management and a research council to retain

the necessary scientific personnel Dr George Baehr, F A C P, New York, N Y, was named a member of the research council

Among the speakers at the recent meeting of the Multnomah County Medical Society, Portland, Ore, May 7, 1941, were

Dr Donald E Forster (Associate), Portland—"Vitamin B Complex",
Dr Merl L Margason, F A C P, Portland—"Migraine"

On June 11, 1941, Dr Russell L Haden, F A C P, Cleveland, Ohio, addressed the Washington County Medical Society, Washington, Pa, on gout

Dr Roy R Snowden, F A C P, Pittsburgh, College Governor for Western Pennsylvania, discussed "Newer Concept of Hypertension" at the meeting of the Cambria County Medical Society at Johnstown, Pa, June 12, 1941

The Rhode Island Medical Society held its annual meeting at Newport, June 1, 1941 Among the speakers were

Dr Willard O Thompson, F A C P, Chicago, Ill—"Sex Hormones Clinical Application",

Dr B Earl Clarke, F A C P, Providence, R I—"Intercapillary Glomerular Sclerosis or Diabetes-Nephrosis Syndrome"

Dr Charles F Gormly, F A C P, Providence, was elected one of the Vice Presidents of the Society at this meeting

The Wisconsin Anti-Tuberculosis Association held one-day institutes on "Diseases of the Chest" in ten towns between July 21 and August 1, 1941 The programs consisted of symposia on roentgen rays, lectures on significance of primary tuberculosis, differential diagnoses of diseases of the chest and pulmonary abscesses, and round table discussions Among the lectures at these institutes were Dr Harold M Coon, F A C P, Statesan, Dr Oscar Lotz, F A C P, Milwaukee, and Dr George C Owen (Associate), Oshkosh

Dr Theodore G Klumpp, F A C P, Chicago, Ill, spoke on "The Philosophy of the Administration of the Drug Sections of the Food, Drug and Cosmetic Act" at the 45th Annual Conference of the Association of Food and Drug Officials of the United States, held at St Paul, Minn, June 9-13, 1941

The Association for the Study of Internal Secretions held its annual meeting in Atlantic City, N J, May 2-3, 1941, under the Presidency of Dr Elmer L Sevringhaus, F A C P, Madison, Wis Dr Edward H Ryneerson, F A C P Rochester, Minn, spoke on "Desoxycorticosterone in Prevention of Surgical Shock"

Dr Henry H Turner, F A C P, Oklahoma City, Okla, was elected Secretary of the Association at this meeting

At the annual meeting of the American Association for the Study of Allergy in Cleveland, Ohio, June 2-3, 1941, Dr Milton B Cohen, F A C P, Cleveland, Ohio, was installed as President. Dr Samuel M Feinberg, F A C P, Chicago, Ill, was named President-Elect, and Dr Oscar Swineford, Jr, F A C P, Charlottesville, Va, Vice-President. Dr James Harvey Black, F A C P, Dallas, Tex, was reelected Secretary.

At the recent annual meeting of the American Association of the History of Medicine held in Atlantic City, N J, Dr Jabez H Elliott, F A C P, Toronto, Ont, was installed as President, and Dr Logan Clendening, F A C P, Kansas City, Mo, was named President-Elect.

Dr Edward A Strecker, F A C P, Philadelphia, Pa, has been elected First Vice-President of the American Neurological Association.

An honorary degree of Doctor of Laws was awarded to Dr Rock Sleyster, F A C P, June 11, 1941, by Marquette University.

ADDITIONAL HOSPITALS APPROVED FOR RESIDENCIES

Dr Hugh J Morgan, Nashville, Tennessee, and Dr O H Perry Pepper, Philadelphia, Pa, are the two appointees by the American College of Physicians on the Conference Committee on Graduate Training in Medicine, the Committee being composed also of representatives from the American Board of Internal Medicine and the Council on Medical Education and Hospitals of the American Medical Association. The Conference Committee at a recent meeting in Cleveland recommended the approval of the following hospitals for residencies in medicine, and this recommendation was accepted by the Council on June 3.

St Francis Hospital, Evanston, Illinois
 Massachusetts Memorial Hospitals, Boston
 Butterworth Hospital, Grand Rapids, Mich
 St Joseph Hospital, Kansas City, Missouri
 St Mary's Hospital, Kansas City, Missouri
 New Rochelle Hospital, New Rochelle, N Y
 St Francis Hospital, Columbus, Ohio
 St Vincent's Hospital, Toledo, Ohio
 Mount Sinai Hospital, Philadelphia
 Presbyterian Hospital, Philadelphia
 Chesapeake and Ohio Hospital, Clifton Forge, Va

THE AMERICAN BOARD OF INTERNAL MEDICINE ANNOUNCEMENT OF EXAMINATIONS

The American Board of Internal Medicine will conduct written examinations October 20, 1941, and oral examinations just in advance of the 1942 meetings of the American College of Physicians and the American Medical Association.

During 1942 written examinations will be conducted February 16 and October 19.

OBITUARIES

DR JAMES ELY TALLEY

American medicine has lost a valued friend in the passing of Dr James Ely Talley, who died July 3, 1941

Dr Talley was a pioneer in the field of cardiology, having founded the cardiac clinic at the Graduate School of Medicine of the University of Pennsylvania and likewise serving as professor of cardiology there from 1921 until he retired in 1938

He was also one of the founders of the American Heart Association and of the Children's Heart Hospital Dr Talley devoted much of his time and tireless energy to both of these enterprises and was always looking forward to a new era when heart disease would remove fewer people from occupations and the mortality rate would be decreased to a minimum

On receiving his M D from the University of Pennsylvania in 1892, Dr Talley entered general practice in West Philadelphia In 1905 he carried on postgraduate study in Berlin, in 1911 he studied in London under Sir James MacKenzie and again in London in 1913 under Sir Thomas Lewis

Being a splendid organizer and possessing the ability of reaching his goal, Dr Talley served in the World War as Lieutenant Commander and in 1919 after being promoted to Commander, Medical Corps, United States Navy, he helped to establish the U S Navy Base Hospital No 5, at Brest, France

Dr Talley has been a Fellow of the American College of Physicians since 1923 Being active in several medical societies, his wise counsel and good fellowship will be missed by his many colleagues He has offered much to the profession by his many articles dealing with internal medicine and cardiology which appeared in various medical journals

Dr Talley was born at Kennett Square, Pennsylvania, July 22, 1864, and died at his home in Lima, Delaware County He is survived by his wife, Isabella, and two nephews, Robert H and John H Andrews Although he was ill for some time, his death is acknowledged with much regret

EDWARD L BORTZ, M D , F A C P ,
Governor for Eastern Pennsylvania

DR JULIUS FRIEDENWALD

Dr Julius Friedenwald was born in Baltimore, December 20, 1866 He died at his home in Baltimore, June 8, 1941

He was a member of the family of Friedenwalds which for two generations has contributed an outstanding part to the medical and cultural life of Baltimore He was a specialist in Gastroenterology and contributed many important clinical observations to his particular field He not only pursued his studies in America, but did a great deal of work abroad He belonged to all the leading medical societies of this country and also published many

papers. He was the co-author of "Diet in Health and Disease," "Dietetics for Nurses," "Secondary Gastrointestinal Disorders," and also contributed to Tice's "Practice of Medicine."

However, the measure of the man could be obtained only from direct contact with him in his daily work. It has been my good fortune to have known the second generation of Friedenwalds, and as an interne to have worked with Dr. Julius Friedenwald. It was apparent that Dr. Friedenwald was more than a specialist, rather in addition a great physician, practicing not only the science of medicine but also the art of medicine, and always equal to any emergency. Equally important was his active interest in the training of young men. For years he regularly invited the younger men to his home for informal discussion of medical problems, and the Julius Friedenwald Fund for research is a memorial to his zeal for research.

His enviable heritage of culture manifested itself in his extramedical activities, in the musical life of Baltimore, and in his interest in charity, both here and in Palestine.

In the passing of Julius Friedenwald, Baltimore medicine has lost one of its medical landmarks. He was loved and respected by all who knew him, and his spirit shall live on through his many pupils.

LOUIS KRAUSE, M D , F A C P ,

Governor for the State of Maryland

DR. HENRY SAMUEL KIESER

Dr. Henry Samuel Kieser, born in Reading, Pennsylvania, July 12, 1903, died very suddenly on July 11, 1941.

Since leaving Hahnemann Medical College in 1930, Dr. Kieser had been primarily interested in Pediatrics. He was Associate in Pediatrics at the Reading Hospital from 1933 to 1938, and also Chief of Pediatrics at the Reading Hospital. He has likewise been Director of Health, Reading Public School System, since 1933.

Dr. Kieser was an energetic and studious young physician with a brilliant future. He had been, for the past year, pursuing graduate work in Pediatrics at the Henry Ford Hospital.

Dr. Kieser was a Diplomate of the American Board of Pediatrics, a member of the Medical Society of the State of Pennsylvania, and a Fellow of the American Medical Association. He had been an Associate of the American College of Physicians since 1940.

Possessing native ability and a pleasing personality, Dr. Kieser was held in esteem by his colleagues and friends, who are shocked by his untimely death.

EDWARD L. BORTZ, M D , F A C P ,

Governor for Eastern Pennsylvania

DR ALEXANDER S DEWITT

Dr Alexander S DeWitt, F A C P , Detroit, died January 2, 1941 He was born in Amsterdam, Holland, in 1882 At an early age he came to this country and obtained his medical training at the University of Michigan Homeopathic Medical School, receiving his degree in 1905 Thereafter, he spent three and one-half years in postgraduate study in Germany and Austria He was formerly Associate Professor of Medicine at the Detroit College of Medicine, Associate Attending Physician at Grace Hospital, and for many years Attending Physician at the Providence Hospital He was a member of the Wayne County Medical Society, Michigan State Medical Society, the American Medical Association, and had been a Fellow of the American College of Physicians since 1920

DR F CLIFTON MOOR

Dr F Clifton Moor, F A C P , Tallahassee, Florida, died February 18, 1941, at the age of 61 He received his Bachelor of Arts degree from the Emory University in 1898 and his degree of Doctor of Medicine from the University of Maryland, School of Medicine, in 1903 For many years Dr Moor was Chief Physician at the Florida State College for Women, and since 1935 had been Director of Student Health and Chief Physician to the Infirmary at this College He was formerly Mayor of the City of Tallahassee, and had taken a very active interest in civic affairs

Dr Moor was a member, past president and secretary of the Leon-Gadsden-Liberty-Wakulla-Jefferson Counties Medical Society, a member and past president of the Florida Medical Association, a member of the Southern Medical Association, a Fellow of the American Medical Association, serving as a member of the House of Delegates during 1934, and had been a Fellow of the American College of Physicians since 1929

DR FRED ELLSWORTH CLOW

Dr Fred Ellsworth Clow, Wolfeboro, New Hampshire, died January 4, 1941 of heart disease He was born October 25, 1881, and graduated from Harvard Medical School in 1904 He pursued postgraduate work at the National Heart Hospital and the Brompton Hospital, London, England, and at the Massachusetts General Hospital in Boston, and at the New York Post-Graduate Hospital, New York City

For many years Dr Clow was a member of the New Hampshire State Board of Registration, Visiting Physician to the Huggins Hospital, Trustee of the New Hampshire State Sanatorium for Tuberculosis, and Consulting Physician to the New Hampshire Soldiers Home He published several articles in leading medical journals, and was a former President of the Carroll County Medical Society In addition, he was a member of the New

Hampshire State Medical Society, a Fellow of the American Medical Association, a Diplomate of the American Board of Internal Medicine, and had been a Fellow of the American College of Physicians since 1934

DR DORAN J STEPHENS

Dr Doran J Stephens (Associate, 1938) died March 19, 1941 Dr Stephens was born in 1903, and received the degree of Bachelor of Arts from the University of Rochester in 1926 He then entered the Medical School of that institution and graduated with the M D degree in 1929 He interned at the Strong Memorial Hospital of the University of Rochester for two years, was Resident Physician at Barnes Hospital, St Louis, from 1931 to 1932, and at the same time was an Assistant in Medicine in the Washington University School of Medicine He then returned to Rochester, New York, where he became Instructor in Medicine at his Alma Mater, and with this institution he was still associated as Assistant Professor of Medicine at the time of his death He was also Assistant Physician to the Strong Memorial Hospital in Rochester

Dr Stephens was a member of Phi Beta Kappa, Sigma Xi, Alpha Omega Alpha, American Society for Clinical Investigation, Society for Experimental Biology and Medicine, the Monroe County Medical Society, the New York State Medical Society, the American Medical Association, and the Rochester Pathological Society He had been an Associate of the American College of Physicians since 1938

His scientific work and investigation which included 45 titles was begun during his medical course and later carried into many fields His last contribution, "The Effects of Pituitrin in Oil," was read before a medical society in Atlantic City during May in *absento de mortem*

ANNALS OF INTERNAL MEDICINE

VOLUME 15

SEPTEMBER, 1941

NUMBER 3

THE BLOOD PRESSURE REDUCING PROPERTY OF EXTRACTS OF KIDNEYS IN HYPER- TENSIVE PATIENTS AND ANIMALS *

By IRVINE H PAGE, M D, O M HELMER, Ph D, K G KOHLSTAEDT,
M D, G F KEMPF, M D, W D GAMBILL, M D, and R D
TAYLOR, M D, *Indianapolis, Indiana*

1 TIGERSTEDT and Bergmann¹ demonstrated that bilateral nephrectomy increases the rise in arterial pressure occurring in anesthetized animals when extracts of kidney containing renin are injected into them. This observation was confirmed by Merrill, Williams and Harrison,² and by Fasciolo, Houssay and Taquini³ who suggested that the increased sensitivity might be due to loss of an anti-pressor substance. Similar increase in sensitivity was observed by Page and Helmer⁴ when angiotonin was administered instead of renin. Angiotonin is the pressor substance resulting from interaction of renin and renin-activator.⁵

Nephrectomy therefore appears to remove the source of some substance which opposes the pressor action of angiotonin.

2 Removal of the normal kidney when the artery of the opposite one is constricted by a clamp or the parenchyma compressed by a perinephric scar, intensifies the hypertension. To explain this, Blalock and Levy⁶ suggested that the normal kidney may destroy the pressor substance causing the hypertension. Fasciolo⁷ shortly thereafter demonstrated that the rise in pressure was more rapid, reached greater heights and was more permanent when the Goldblatt clamp was applied to the remaining kidney in a dog which had been uninephrectomized. He also demonstrated that normal kidneys opposed the action of a hypothetical pressor substance by showing that a greater rise in arterial pressure occurred in nephrectomized dogs than in normal ones when blood perfusing an ischemic kidney was allowed to enter their circulation.

* Lecture given before the Third General Session of the American College of Physicians, April 22, 1941, Boston, Massachusetts

From the Lilly Laboratory for Clinical Research, Indianapolis City Hospital, Indianapolis Indiana

Copyright, 1941, by The American College of Physicians

Katz, Friedman, Rodbard and Weinstein⁸ formulated the belief that the intensity of the hypertension depends on the presence of normal renal tissue. They suggested that there is a direct relationship between the height of the blood pressure and the ratio of "ischemic" to normal tissue and that the antagonistic action of normal renal tissue is due to its metabolic and not its excretory activity.

3 Plasma from animals in which sufficient amounts of renin were injected to cause them no longer to respond with rise in arterial pressure (tachyphylaxis) does not cause vasoconstriction in the isolated rabbit's ear when perfused with added renin (Page⁹). More important, even the addition of renin-activator does not impair vasoconstrictor properties. Contrariwise, normal blood with added renin causes marked vasoconstriction. Administration of renin thus appears to cause the release of a substance in the intact animal which antagonizes renin or its reaction product, angiotonin. On this basis our conception of anti-pressor substances arose.

4 Plasma of nephrectomized animals when mixed with angiotonin and renin and perfused through a rabbit's ear causes much greater vasoconstriction than normal plasma (Page and Helmer⁴). The removal of the kidneys has thus removed the factor which opposes the action of angiotonin. This factor is evidently humoral since it can be transferred from the intact animals to the isolated perfused rabbit's ear.

5 Hypersensitivity to the pressor action of angiotonin and renin induced by nephrectomy can be temporarily abolished by transfusion of large amounts of normal blood into the nephrectomized animal. Normal blood, therefore, contains an inhibitor substance⁴. According to Freeman¹⁰ direct transfusion of from 25 to 200 c c of normal blood into hypertensive dogs produces a fall in pressure ranging from 6 to 25 per cent lasting 6 to 31 minutes. Blood from normal and hypertensive human donors transfused into normal and hypertensive recipients respectively caused no fall in arterial pressure.

6 Renal extracts have been prepared which, when given by mouth, diminish partially the response of normal rats to the pressor action of renin, ephedrine and pitressin¹¹. The increased sensitivity of nephrectomized dogs to angiotonin and renin can be abolished by parenteral injection of renal extract¹².

These observations suggested that a substance is contained in renal tissue which might oppose the pressor action of angiotonin or similar pressor agents and result in reduction of arterial pressure. Attempts to extract such an inhibitor or antipressor substance have, we believe, been successful both in the hands of Grollman, Harrison and Williams,¹³ and in ours¹⁴. The evidence at present available indicates that we are dealing with the same principle as that reported shortly before by Harrison, Grollman and Williams (Our work was based on different reasoning and was done independently. The two groups are now collaborating toward a further solution of the problem.) It is of great interest that their material is active by mouth in

rats, dogs and man, most of their best results having been obtained by this mode of administration. Our work has been limited to parenteral methods of administration.

PREPARATION OF RENAL EXTRACTS

Methods for the preparation of these extracts have already been published by Grollman, Williams and Harrison¹⁵ and by us^{16, 17}. In principle, the method we have employed consists of extraction of ground fresh kidneys with acetic acid—salt solution, heating the mixture to 56° C and precipitating the filtrate with ammonium sulfate between 0.25 and 0.6 saturation. This precipitation is repeated twice and the product dialyzed free of ammonium sulfate. Extraction of this product with ether to remove lipids appears to decrease the number of reactions produced and certainly reduces the local tissue irritation. This step had not been previously employed. It is then sterilized by filtration through a Seitz filter.

THE EFFECT OF INJECTION OF RENAL EXTRACTS IN HYPERTENSIVE DOGS

Dogs were made hypertensive by the silk perinephritis method¹⁸. Blood pressure was measured daily by direct femoral intra-arterial puncture, and the pressure recorded on a smoked drum from a mercury manometer. When the mean arterial pressure was over 180 mm Hg, and remained steadily above this figure for a week, the dog was used for assaying the potency of the renal extracts.

It was found convenient in the preparation of hypertensive animals to wrap the left kidney in silk and remove the other kidney at the same time. In alternate animals, both kidneys were wrapped in silk. The blood pressure in the animals in which one kidney has been wrapped in silk and the other kidney removed usually rises more rapidly and to more extreme heights. The incidence of the malignant syndrome is greater among them. The blood pressure in the second group rises more slowly and tends to remain more steadily at the elevated pressure without as frequent complication by the appearance of the malignant syndrome. Both types of hypertension are useful for assay purposes. Two hundred and eighty hypertensive dogs have been treated with renal extracts.

Extracts were usually injected subcutaneously. In dogs they cause little local reaction and no general ones. No immediate change in arterial pressure is observed. In from two to four days the fall begins and its rapidity depends in large measure on the amount of extract given.

Extract prepared from 400 to 900 grams of fresh pork kidney is usually required to reduce the blood pressure of a 12 kilo dog from 200 to 130 mm Hg. If much larger doses are given a shock-like syndrome appears which has been well described by Harrison, Grollman and Williams¹¹. The animal loses its appetite, becomes weak, and tachycardia appears. This is followed,

after the blood pressure has fallen to 70 mm Hg or lower, by oliguria or anuria, bloodlessness of the extremities, and elevated blood urea nitrogen.

The fall in arterial pressure is usually gradual if the extract is given in moderate doses daily, the pressure reaching normal or near normal levels in five to eight days. If the extract is now discontinued the blood pressure may remain low for several days and in unusual cases for weeks and gradually rise to its original hypertensive level. Some dogs require more extract to reduce this blood pressure than do others. This phenomenon does not ap-

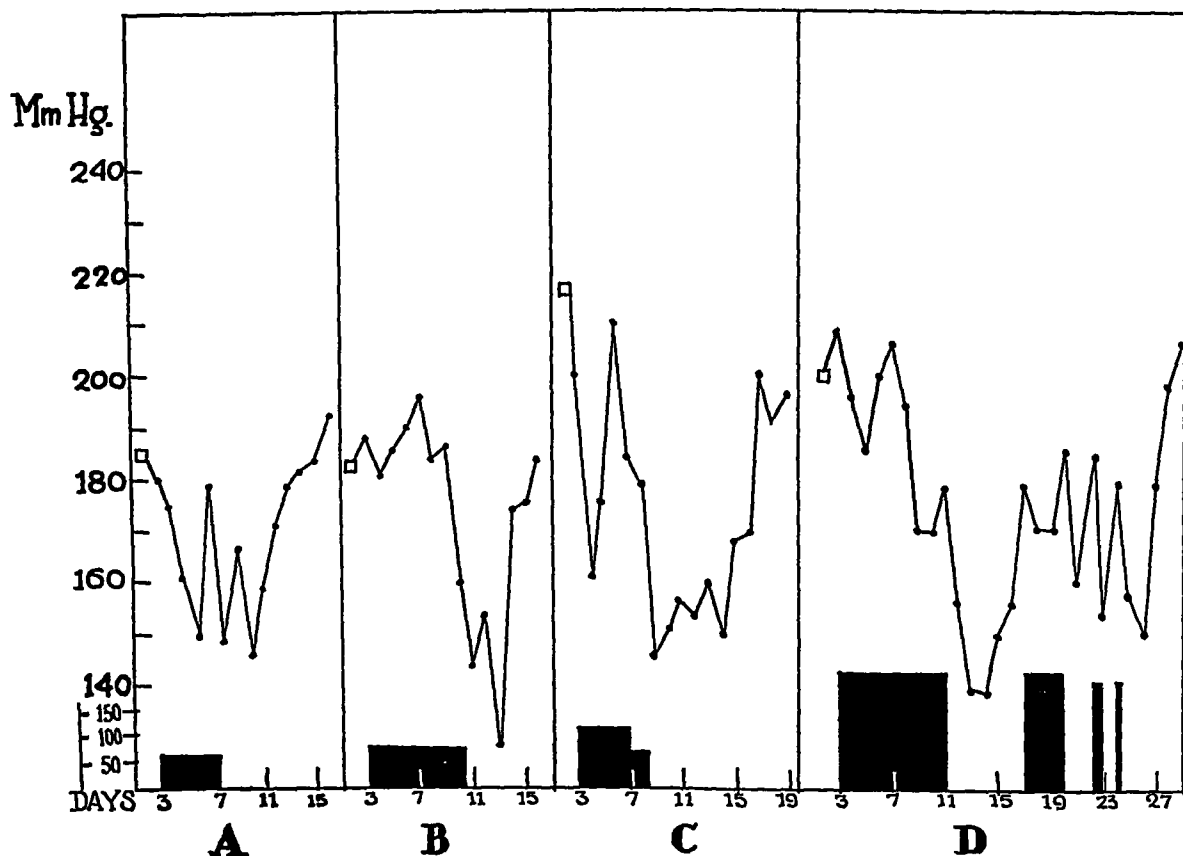


FIG 1 *Dog 5-87* Female, weight 102 kilos. The effect of four renal extracts on arterial pressure. Arterial pressure is expressed in mm Hg (ordinate) and time in days (abscissa). \square represents the average arterial pressure during 10 days before extract was given. Daily dosage of extract is expressed by height of shaded area (ordinate) as grams of kidney used in preparation of extract and given per kilo of body weight.

A—Renal extract prepared by 0.3 to 0.8 saturation with ammonium sulfate. Hypertension had been present 3 months before extract was administered.

B—Renal extract prepared by extraction at pH 4.0 with 2 per cent saline and heated to 56°. C—Filtrate saturated with ammonium sulfate and precipitate dissolved in water and dialyzed. An interval of 7 months elapsed between A and B.

C—Renal extract prepared by twice precipitating with ammonium sulfate and treatment with barium hydroxide and dialysis. An interval of 5 months elapsed between B and C. Blood urea nitrogen, on fourth day extract was given, was 17 mg per 100 cc. Day after administration of extract was completed and when maximum reduction of blood pressure was observed, blood urea nitrogen was 21 mg per 100 cc.

D—Renal extract was from pooled lot of extracts which had been prepared by precipitating three times with ammonium sulfate. An interval of 4 months elapsed between C and D. Blood urea nitrogen on first day of administration of this extract was 70 mg per 100 cc, on the last day of administration of extract, blood urea was 147 mg per 100 cc. Four days after extract had been stopped blood urea nitrogen was 71 mg per 100 cc.

TABLE I
The Effect on Blood Urea Nitrogen of Reduction of Arterial Pressure by Kidney Extract in Hypertensive Dogs

Dog No	Before Renal Extracts		Maximum Reduction of Arterial Pressure				Effect of Spontaneous Return of Arterial Pressure to Hypertensive Levels			
	Arterial Pressure mm Hg	Blood Urea Nitrogen in mg /100 c c	Arterial Pressure mm Hg	Blood Urea Nitrogen in mg /100 c c	No Days to Reduce Arterial Pressure	Evidence of Malignant Hypertension		Arterial Pressure mm Hg	Blood Urea Nitrogen in mg /100 c c	No Days Required for Rise in Arterial Pressure and Change in B U N
						Bloody Diarrhea	Retinal Detachment			
Group I No Significant Change of Blood Urea Nitrogen or Fall										
8-76	224	24	96	26	2	—	—	178	29 8	30
9-38	216	28 6	146	24 2	11	—	bilateral	208	58 7	13
12-37	180	44 5	164	27	6	++	—	204	71 5	3
10-21	212	49 6	156	14 2	3	++	bilateral	174	22 9	3
12-80	210	34	154	18 6	4	—	—	210	—	—
11-78	184	14 1	144	11 4	7	—	—	166	—	—
13-22	208	32 6	140	27	2	—	+	224	—	—
9-80	200	18	140	12 8	7	+	unilateral	188	21 4	5
10-21	188	17	150	22 8	5	—	bilateral	178	34	12
	206	31	138	36	2	—	—	210		
Group II Significant Rise in Blood Urea Nitrogen										
13-05	180	28 6	142	53 8	2	—	bilateral	166	49 5	3
12-24	192	15 6	98	136	5	+	bilateral	190	42 5	6
7-52	200	49	80	112	4	++	++	—	—	—
7-83	230	25 4	124	75	2	+	—	178	29 7	8
5-87	208	69	140	147	2	—	—	166	71 5	4
8-76	224	20	138	37	4	—	—	160	38	5

pear to be directly related to the initial height of the blood pressure. It is for this reason that three or more dogs may be required for the assay of each extract.

The effect on renal function is often striking. Corcoran and Page¹⁹ found that injections of inhibitor into normotensive dogs caused relaxation of the glomerular efferent arteriole and usually an increase in renal blood flow. No change in blood pressure occurred in these animals unless very large doses were given. In hypertensive dogs reduction of blood pressure to levels of about 150 mm Hg was associated initially with rise in blood flow but if the pressure continued to decline, the blood flow fell precipitously to return to higher levels as arterial pressure increased. Renal extracts thus appeared to oppose the renal action of substances such as angiotonin, for it had been shown^{20, 21} that angiotonin sharply reduced blood flow chiefly by constricting the glomerular efferent arterioles.

The effect on blood urea nitrogen is variable (table 1). The more usual effect is a fall, but no significant change may occur. The less usual is a

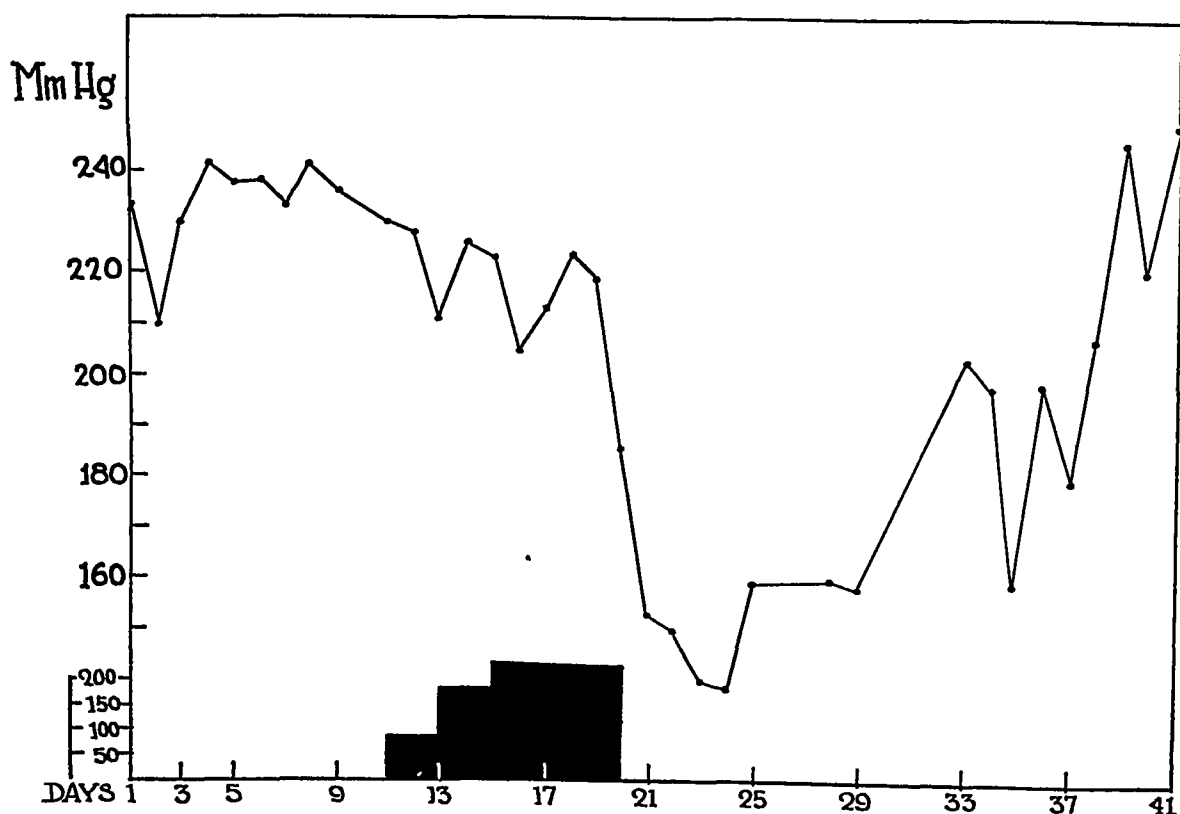


FIG 2 Dog 8-76. Weight 92 kilos. The effect on arterial pressure of renal extract prepared by precipitation with ammonium sulfate and treatment with barium hydroxide and dialysis. Arterial pressure is expressed in mm Hg (ordinate) and time in days (abscissa). Daily dosage of extract is expressed in grams of kidney used in its preparation and given per kilo of body weight and is represented in the figure by height of shaded area (ordinate). Hypertension had been present five months. During last three months retinal hemorrhages and detachment were observed while animal received six different kidney extracts. The results produced by the seventh extract are shown in the figure. Blood urea nitrogen on second day extract was administered was 20 mg per 100 c c, on last day of administration it was 22 mg per 100 c c. Three days after extract was stopped blood urea nitrogen was 37 mg per 100 c c and eleven days later it was 38 mg per 100 c c.

pronounced rise in blood urea which falls again when the arterial pressure spontaneously resumes its hypertensive level. There appears to be no relationship between these changes and the occurrence of the malignant syndrome.

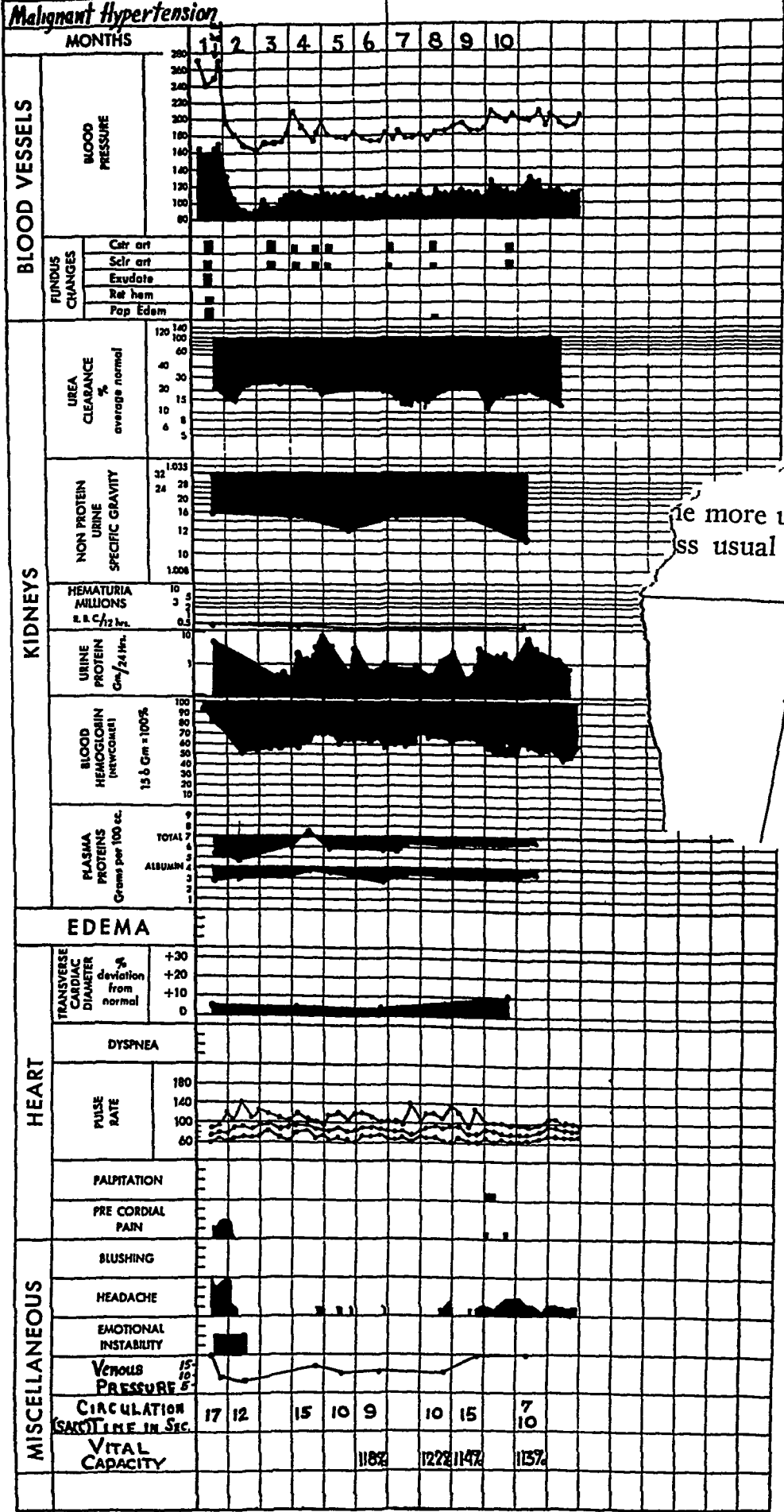
Many of the dogs with experimental hypertension exhibit the malignant syndrome. This consists of loss of appetite, early blindness with detachment of the retina, papilledema and massive intra-ocular hemorrhages. The animals become weak, have severe bloody diarrhea, vomiting, pulmonary edema, hematuria, anuria, rapidly progressive anemia, and convulsions. Death usually occurs within several days, but in unusual cases it may be much longer. If treatment is not started too late, many of these animals can be saved. The syndrome often reappears when the injections of inhibitor are discontinued and may again be counteracted by further administration of kidney extract. The blood urea nitrogen, which usually is initially very high, usually falls as the blood pressure falls and clinical improvement occurs. Vision returns, associated with reattachment of the retina, subsidence of the papilledema and resorption of the hemorrhages. Regression of the other signs such as bloody diarrhea is clearly evident. Much the same results have been obtained in rats with experimental hypertension. They too exhibit the malignant syndrome, and its reversal is also observed when inhibitor is injected.

EFFECT OF RENAL EXTRACTS ON PATIENTS

The history and certain laboratory data are presented in the following abstracts. The figure which accompanies each abstract is a bedside chart and exhibits in graphic form the most pertinent of the observations made on the patients. It is important for the reader to have a clear notion of the way in which they are prepared to avoid misinterpretation.

An attempt is made when it appears to have any chance of success of estimating the length of time the hypertension has existed, and this is represented by the figures in the line parallel with the word "Months". The blood pressure measurements are usually single determinations until the patient either entered our clinic or was admitted to the hospital. After admission, the patient was put to bed and the arterial pressure was measured twice daily. The blood pressure readings are averaged over a period of a week. One dot on the chart represents such an average. Where such average pressures begin on the chart can be ascertained by noting when urea clearance was determined. It is rare that the patients were not allowed up after a week or more of treatment and in most cases they were transferred to the out-patient department. For this reason the control blood pressure levels taken at complete bed rest should be abnormally low compared with the level taken when the patient is either up and about or outside the hospital.

Fundus changes are indicated under the following headings, employing a semi-quantitative scale of + to ++++ to grade them: (1) arteriolar constriction, (2) arteriolar sclerosis, (3) exudates, (4) retinal hemorrhages,



to
thus
or it
by

le more usual
ss usual is a



and (5) papilledema Urea clearance, as determined by the modification described by Van Slyke, Page, Hiller, and Kirk²² of the original method, is expressed as average per cent of normal The ability to concentrate urine maximally is ascertained by withholding water from the patient for 24 hours and measuring the specific gravity of the urine passed after the last 12 hours Correction is made for the gravity contributed by protein in the urine Hematuria is determined by counting the red cells in the urine according to the technic of Addis²³ Values above 500,000 in a 12 hour specimen are considered abnormal Plasma proteins were determined by the method of much²⁴ The black areas representing edema have the following significance: Height of black area in quarters of total space (1) trace, (2) moderate, (3) marked pitting, (4) general edema with ascites The trans-kidney cardiac diameter is recorded as the per cent deviation from normal high, usually the table of Ungerleider and Clark The circulation time was Vision returns, intravenous injection of 2.25 gm of soluble saccharin in 5 c c papilledema and The arm-to-tongue time is measured in seconds The signs such as blood considered from 7 to 10 seconds and borderline normal from been obtained in r Venous pressure is recorded in centimeters of blood malignant syndrome content of the blood was ascertained by the method of injected erson,²⁵ and recorded as mg in 100 c c of blood

F MALIGNANT HYPERTENSION

The history

CASE REPORTS

abstracts The

Case 1 R T (703) This 24-year-old man complained of severe headaches and blurring of vision At 12 years of age he had scarlet fever During the preceding winter he had headaches regularly Two weeks before admission he fell and hit the back of his head A severe headache immediately occurred and persisted At this time his blood pressure was found to be elevated Vision in the left eye rather suddenly became so poor that he was unable to read, and the vision in the right one seemed to be deteriorating

The patient appeared acutely ill, his face was drawn and anxious The right side of his face twitched A subconjunctival hemorrhage was seen in the right eye Grade 3 papilledema, grade 4 exudates, grade 2 hemorrhages, and grade 3 constriction were observed in the eyegrounds The heart was slightly enlarged (+5 per cent deviation) Venous pressure was 22 cm in terms of normal salt The electrocardiogram showed inversion of the T-waves in Leads I, II, III, and IV

The clinical improvement in this man was remarkable Shortly after admission acute glaucoma occurred Reduction of the blood pressure by kidney extract appeared to aid in resolution of the process

This patient has remained hospitalized for economic reasons, but is up and about Optic fundi now reveal grade 2 constriction and sclerosis of the retinal arterioles Electrocardiogram exhibits upright T-waves in all leads He has been treated with kidney extract continuously for the past 11 months

Case 2 (769) The arterial pressure of this 47-year-old white male was found to be 140 mm Hg systolic and 90 mm diastolic seven months ago Five months ago it was 160 mm Hg systolic and 90 mm diastolic He complained of headaches, convulsive seizure with loss of consciousness, and almost complete blindness

No.		Hosp. No 769		w ⁶ 47 yrs.		ht 5'6 1/2 cm.		Weight		775 kg.			
MALIGNANT HYPERTENSION													
MONTHS		1 3 4 5 6 7 8 9 10 11											
BLOOD VESSELS	BLOOD PRESSURE												
		FUNDUS CHANGES											
			Ctr art										
			Scler art										
			Exudate										
KIDNEYS	UREA CLEARANCE % average normal												
	NON PROTEIN URINE SPECIFIC GRAVITY												
	HEMATURIA MILLIONS R.B.C./12 Hrs.												
	URINE PROTEIN Gm/24 Hrs.												
	BLOOD HEMOGLOBIN (Hctwcones) 15.6 Gm = 100%												
	PLASMA PROTEINS Grams per 100 cc. TOTAL ALBUMIN												
HEART	EDEMA												
	TRANSVERSE CARDIAC DIAMETER % deviation from normal												
	DYSPNEA												
	PULSE RATE												
	PAUSETION												
MISCELLANEOUS	PRE CORDIAL PAIN												
	BLUSHING												
	HEADACHE												
	EMOTIONAL INSTABILITY												
	Venous Pressure cm. of Blood												

Physical findings at the time of admission to the Lilly Clinic were arterial blood pressure 200 mm Hg systolic and 120 mm diastolic, ocular fundi revealed grade 4 constriction and sclerosis of retinal vessels, grade 4 hemorrhages, exudates, and papilledema

Urea clearance was 90.5 per cent of average normal, maximal ability to concentrate urine was 1,023, electrocardiogram was normal

Arterial blood pressure average for first week at bed rest was 208 mm Hg systolic and 121 mm diastolic. Kidney extract was administered intramuscularly. The arterial blood pressure averaged 197 mm Hg systolic and 115 mm diastolic for first week of treatment. He was treated for eight weeks, and the blood pressure now averages 166 mm Hg systolic and 99 mm diastolic. He now reads newspapers and is symptom free. Ocular fundi show grade 3 constriction and sclerosis, grade 1 exudates and hemorrhages, and grade 2 papilledema.

He has had two shock-like reactions and one bout of chills and fever.

Case 3 M B (764) A colored, 35-year-old female complained of protracted headaches, nausea and vomiting, blurring of vision, and dyspnea. Hypertension was discovered five years ago.

On admission to the Lilly Clinic arterial blood pressure was 260 mm Hg systolic and 140 mm diastolic. Retinal vessels displayed grade 4 constriction and sclerosis. Ocular fundi revealed grade 3 hemorrhages, grade 1 exudates and papilledema. Heart was enlarged to 11 cm to left of midline. There was a soft systolic blow at the cardiac apex.

Urea clearance was 44.9 per cent of average normal, maximal ability to concentrate urine was 1,020, proteinuria amounted to 0.8 gm per 24 hours, blood hemoglobin was 70 per cent of average normal. Retrograde pyelograms were negative. The electrocardiogram displayed left axis deviation, biphasic T-waves in Leads I, II, and IV.

Arterial blood pressure averaged 235 mm Hg systolic and 137 mm diastolic for the first week in the hospital. Kidney extract was administered. The arterial blood pressure average for the first week of treatment was 200 mm Hg systolic and 115 mm diastolic. This was maintained at a slightly lower average of 187 systolic and 110 mm diastolic. She became symptom free. The eyegrounds revealed grade 3 constriction and grade 4 sclerosis of retinal vessels. Hemorrhages, exudates, and papilledema entirely disappeared. T-waves in Leads I, II, and IV of electrocardiogram became upright.

This patient suffered one shock-like reaction and almost weekly chills and fever.

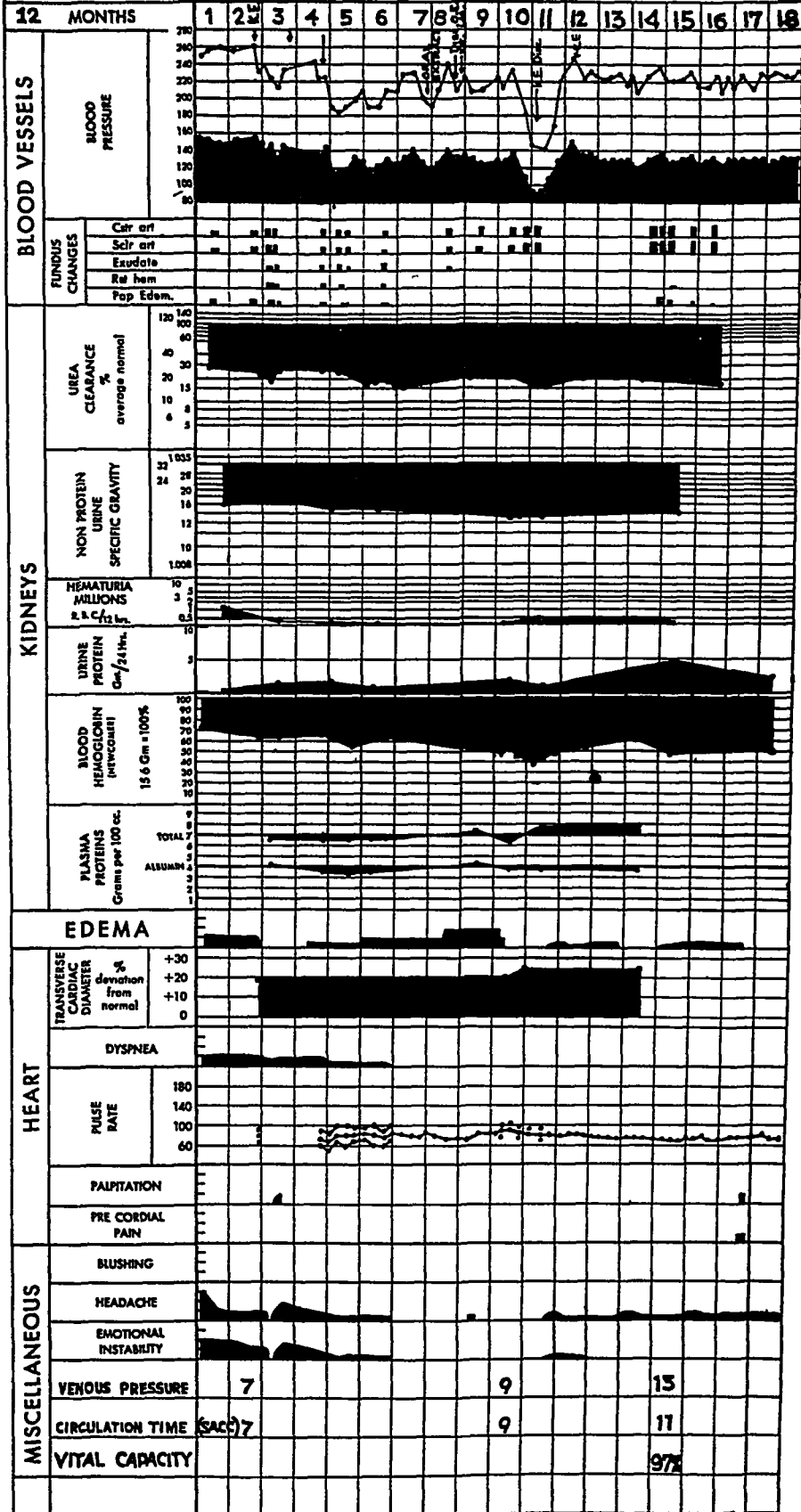
Case 4 C R (671) A colored female, aged 36, complained of headaches, failing vision, and nocturia of about 10 months' duration. These symptoms progressed until she was unable to read.

Grade 2 arteriosclerosis and constriction of the retinal arterioles were found and grade 2 papilledema. Blood pressure was 256 mm Hg systolic and 152 mm diastolic. Grade 1 edema was present. Urea clearance had already fallen to 30 per cent of normal and was continuing to fall. The Addis count revealed a marked increase over normal of the red blood cells in the urine. The cardiac diameter showed +14 per cent deviation from normal. The electrocardiogram exhibited isoelectric T-waves in Leads I and II (Feb 28, 1940), which eight days later became inverted.

While resting in bed the blood pressure averaged 233 mm Hg systolic and 140 mm diastolic. Retinal hemorrhages were appearing in crops. Beef muscle extract was administered intramuscularly and the blood pressure fell to 188 mm Hg systolic and 118 mm Hg diastolic. After discontinuing this extract the pressure rose to 237 systolic and 143 mm diastolic. The patient was discharged from the clinic and readmitted a month later. The blood pressure average was 224 mm Hg systolic and 130 mm diastolic. Kidney extract was administered and the blood pressure fell within

No. M.B.		Hosp No 764		c of 35 yrs.		ht 5'6 1/2 cm.		Weight 137 lb. kg.							
MALIGNANT HYPERTENSION															
		MONTHS		<div style="display: flex; justify-content: space-between;"> 1 15 52 54 55 56 57 </div>											
BLOOD VESSELS	FUNDUS CHANGES	BLOOD PRESSURE													
										Cdr art					
										Scl art					
										Exudate					
										Ret hem					
Pap Edem															
KIDNEYS	UREA CLEARANCE %														
	NON PROTEIN URINE SPECIFIC GRAVITY														
	HEMATURIA MILLIONS R.B.C./12 hr.														
	URINE PROTEIN Gm./24 hr.														
	BLOOD HEMOGLOBIN (NEWCOMER) 15.6 Gm = 100%														
	PLASMA PROTEINS Gram per 100 cc.														
	ALBUMIN														
HEART	EDEMA														
	TRANSVERSE CARDIAC DIAMETER % deviation from normal														
	DYSPNEA														
	PULSE RATE														
	PAUPTATION														
	PRE CORDIAL PAIN														
MISCELLANEOUS	BLUSHING														
	HEADACHE														
	EMOTIONAL INSTABILITY														
	Venous Pressure cm of Blood														
	Circulation Time Saccharin														
	Vital Capacity % of Normal														

EARLY MALIGNANT HYPERTENSION



No. 662 -		Hosp No L.S. 6		41 yrs. ht 173 cm.		Weight 89.8 kg.		
MALIGNANT HYPERTENSION								
6 MONTHS								
BLOOD VESSELS	BLOOD PRESSURE							
		FUNDUS CHANGES						
KIDNEYS	UREA CLEARANCE % average normal							
	NON PROTEIN URINE SPECIFIC GRAVITY							
	HEMATURIA MILLIONS R. & C./12 hr.							
	URINE PROTEIN Gm/24 hr.							
	BLOOD HEMOGLOBIN (newcomer) 15 G Gm = 100%							
	PLASMA PROTEINS Grams per 100 cc							
HEART	EDEMA							
	TRANSVERSE CARDIAC DIAMETER % deviation from normal							
	DYSPNEA							
	PULSE RATE							
	PAUPTATION							
MISCELLANEOUS	PRE CORDIAL PAIN							
	BLUSHING							
	HEADACHE							
	EMOTIONAL INSTABILITY							
	Venous Pressure							
Circulation Time								

two days to an average of 195 mm Hg systolic and 124 mm diastolic and continued down to 185 mm Hg systolic and 117 mm diastolic

Urea clearance was low (16 per cent) and did not change significantly during treatment. It is of interest that the T-waves which were inverted in Leads I and II became upright. Retinal hemorrhages, exudates, and papilledema disappeared.

After five months of treatment, dependent edema and headaches prompted re-admission to the Lilly Clinic for intensive kidney extract therapy. During first week of treatment, blood pressure averaged 189 mm Hg systolic and 115 mm diastolic. She developed an abscess in her hip that was accompanied by a septic fever to 104° daily. Blood pressure fell to 126 mm Hg systolic and 74 mm diastolic. She complained of light headedness. Renal extract was discontinued and the lesion was incised and drained. The next three weekly blood pressure averages were 148 mm Hg systolic and 92 mm diastolic, 141 mm systolic and 91 diastolic and 168 mm systolic and 104 mm diastolic. She was discharged to out-patient department. Without renal extract blood pressure rose to 246 mm Hg systolic and 146 mm diastolic. Extract treatment was started again and blood pressure has averaged 210 to 230 mm Hg systolic and 120 to 130 mm Hg diastolic. She has resumed her household duties and has only occasional headaches.

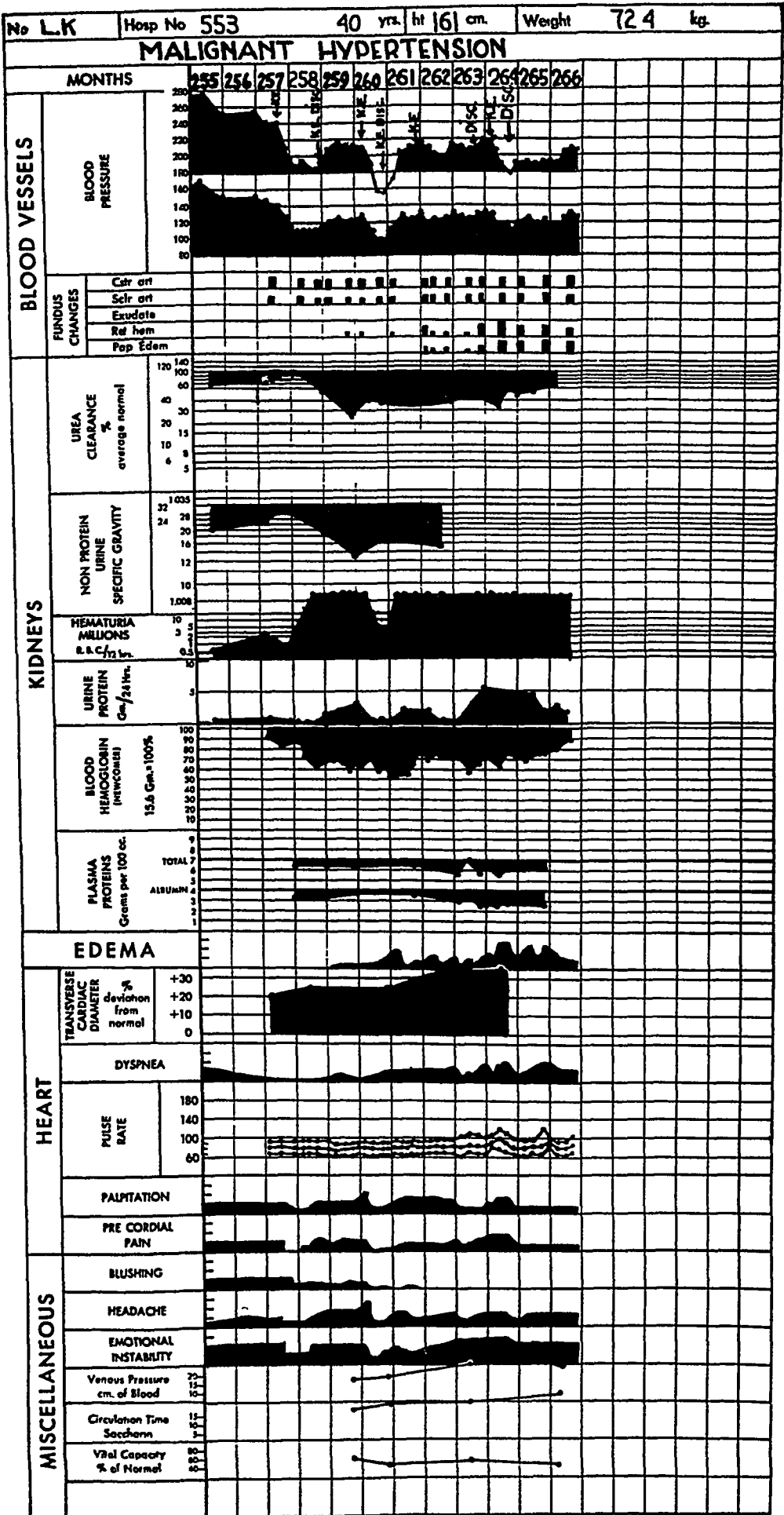
Case 5 L S (662) This 41-year-old man complained of dyspnea, headache, insomnia, nausea and vomiting, edema of the legs, and swelling of the abdomen. He knew that he had hypertension for four years, but two years before admission dyspnea and fatigability became pronounced. On admission he exhibited cyanosis of the extremities, orthopnea, grade 4 edema, and ascites. The eyegrounds showed grade 3 sclerosis and constriction of the vessels, grade 3 hemorrhages, exudates, and papilledema. The heart was markedly enlarged (+ 39 per cent deviation), the rate was rapid, and gallop rhythm was present. The venous pressure was elevated (12 cm of blood), and many moist râles were heard in the chest. The electrocardiogram demonstrated numerous extrasystoles, depression of the S-T segment in Leads I, II, and III, inverted, splintered QRS in Lead III and biphasic QRS in Lead IV.

During the first four weeks after admission the blood pressure averaged 215 mm Hg systolic and 150 mm diastolic. The week following administration of kidney extract the pressure averaged 178 mm Hg systolic and 110 mm diastolic. He complained of less dyspnea, and the rhythm of the heart became regular. The papilledema receded. Extract was discontinued, and the blood pressure rose to near its former level, the pulse became irregular and rapid, and dyspnea returned. Urea clearance began to fall, and retinal hemorrhages appeared along with papilledema. A more purified but evidently weaker extract was again administered. The patient, however, became stuporous and complained of severe joint pains. Urea clearance continued to fall, and massive hemorrhages occurred from the bowel. The latter continued and apparently were the immediate cause of death. The diagnosis of malignant hypertension was confirmed at autopsy. The bleeding was coming from ulcers in the large bowel.

Case 6 (553) A white female, aged 38 years, complained of palpitation, headaches, insomnia, and precordial pain. Hypertension was discovered 21 years ago. In 1936, because of the severity of the hypertension, both splanchnic nerves were resected but within two weeks the pressure had risen to 190 mm Hg systolic and 135 mm diastolic. On admission to the Lilly Clinic in 1938 blood pressure was 248 mm Hg systolic and 148 mm diastolic. Maintenance doses of digitalis were being given before her admission because, on discontinuing it, decompensation occurred. Despite the long continued hypertension, the renal function was good.

Administration of thiocyanate for a period of 10 months brought no significant reduction of blood pressure.

Kidney extract administration was started six months ago. At first the extracts were not as potent as those now employed and the fall in blood pressure was cor-



respondingly smaller. The average blood pressure over several years before administration of extract was 230 mm Hg systolic and 134 mm diastolic and after extract it had fallen to 172 mm. systolic and 104 mm diastolic.

Because of inflammatory and fibrotic changes in the hips at the sites of earlier crude renal extract injections, therapy was discontinued and started again on several occasions. The rise and fall in blood pressure averages are noted on the graphic chart. Six months ago papilledema and retinal hemorrhages appeared in the ocular fundi, accompanied by gross hematuria, indicating onset of malignant hypertension. Eye ground changes were reversed and hematuria was reduced following kidney extract administration and reduction of the arterial pressure to averages of 155 mm Hg systolic and 94 mm diastolic. Again the damaged tissues of patient's buttocks necessitated termination of treatment. Rectal administration of renal extract failed to maintain desired blood pressure levels. Hemorrhages and papilledema again occurred in the eyegrounds. Cardiac decompensation has resumed and it was deemed unwise to continue extract treatment because of the many complications.

Case 7 This white male, aged 34, complained of headaches, and failing vision of about 18 months' duration. Vision became suddenly diminished. The headaches became so severe that it was necessary to give large amounts of codeine.

The patient appeared very ill. He was unable to read. Examination of the eyegrounds showed grade 3 constriction and sclerosis of the arterioles, grade 3 papilledema and exudates, and grade 2 hemorrhages. The heart was slightly enlarged (+14 per cent deviation). The S-T segments in Leads I, II, and III were depressed and the QRS complex was splintered in Lead III.

Shortly after admission the patient had a series of four convulsions. The arterial blood pressure was 278 mm Hg systolic and 170 mm diastolic and spinal fluid pressure 200 mm of water. Severe vomiting then began, and all fluids had to be given by rectum. The patient became irrational. Since the outlook seemed so poor, kidney extract was administered. The blood pressure fell progressively. Without extract the diastolic pressure was seldom below 158 mm Hg and often much higher, while with it, it was seldom above 130 mm Hg. Hemorrhages disappeared from his eyegrounds, and the papilledema regressed so that he was able to read. Urea clearance was 13 per cent of normal when treatment was started and did not appear affected by it. Headaches were much reduced in severity.

Since we did not believe that the extremely low renal function was reversible, we could not conscientiously advise him to continue treatment. When it was discontinued and the patient allowed to go home, the blood pressure rose sharply, and he died within two weeks.

Case 8 E P (722) This 46-year-old colored patient noticed that two years ago she became short of breath on slight exertion, and one year ago swelling of her feet and ankles occurred. Exertion brought on attacks of a smothering feeling in her chest and severe palpitation. Ten days before admission mild apoplexy occurred followed by moderate left hemiplegia. Nocturia became persistent. Anginal pains also occurred on even slight exertion.

The patient is obese. Eyegrounds showed grade 3 constriction, sclerosis, exudates, papilledema, and hemorrhages, both fresh and old. Blood pressure on admission was 310 mm Hg systolic and 124 mm diastolic. The heart was enlarged (27 + per cent deviation). The T-waves in Leads I, II, III, and IV were inverted, the P-wave in Lead III isoelectric. Urea clearance was 70 per cent of normal. Vital capacity was reduced to 40 per cent of normal. Retrograde pyelograms show that there was bilateral hydronephrosis, but cultures of the urine were negative.

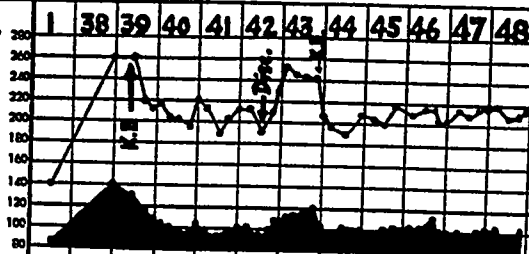
Kidney extract was administered after the blood pressure had been stabilized at an average level of 260 mm Hg systolic and 136 mm diastolic. During the next week it had fallen to an average of 216 mm Hg systolic and 103 mm diastolic, the

MALIGNANT HYPERTENSION

MONTHS

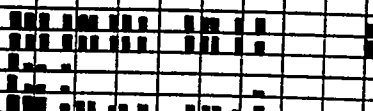
BLOOD VESSELS

BLOOD PRESSURE



FUNDUS CHANGES

Ctr art
Scir art
Exudate
Ret hem
Pap Edem



KIDNEYS

UREA CLEARANCE % average normal

120
100
80
60
40
20
10
5



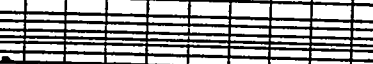
NON PROTEIN URINE SPECIFIC GRAVITY

1.035
1.030
1.025
1.020
1.015
1.010
1.008



HEMATURIA MILLIONS R.B.C./12 Hrs.

10
5
0.5



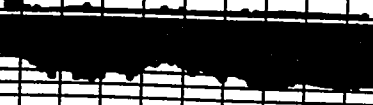
URINE PROTEIN C₅₀/24 Hrs.

10
5
0.5



BLOOD HEMOGLOBIN (HwCO₂) 15.6 Gm = 100%

100
80
60
40
20
10



PLASMA PROTEINS Grams per 100 cc.

TOTAL
ALBUMIN



EDEMA

TRANSVERSE CARDIAC DIAMETER % deviation from normal

+30
+20
+10
0

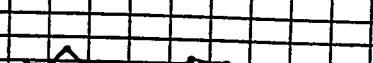


DYSPNEA



PULSE RATE

180
140
100
60



PALPITATION

PRE CORDIAL PAIN

BLUSHING

HEADACHE

EMOTIONAL INSTABILITY

Venous Pressure cm. of blood

30
15
0



Circulation Time Seccharin

15
10
5
0



Vital Capacity % of Normal

80
60
40
20
0



second week 205 mm Hg systolic and 100 mm diastolic, the third week 202 mm Hg systolic and 100 mm diastolic, and the fourth week 202 mm Hg systolic and 97 mm diastolic. Marked regression of the eyeground changes occurred. There was less exudate and only a small amount of hemorrhage. Proteinuria diminished from 3 gm in 24 hours to less than 0.1 gm. Hemoglobin was not changed significantly (70 per cent). The electrocardiogram, taken three weeks after treatment was initiated, showed inversion of the T-waves in Leads I, II, and III but not in Lead IV.

After two months of kidney extract the weekly arterial blood pressure average was 191 mm Hg systolic and 88 mm diastolic. The patient had no complaints. The optic fundi revealed grade 3 constriction and sclerosis of retinal arterioles with grade 2 papilledema and no hemorrhages or exudates. Kidney extract was discontinued, and arterial blood pressure average for the first week was 252 mm Hg systolic and 110 mm diastolic, second week 230 mm Hg systolic and 107 mm diastolic, and third week 246 mm Hg systolic and 115 mm diastolic. Kidney extract therapy was resumed, the arterial blood pressure average for the week was 209 mm Hg systolic and 99 mm diastolic, the second week was 196 mm Hg systolic and 94 mm diastolic.

After approximately eight months of kidney extract therapy patient has no complaints and leads a rather quiet home life. Weekly arterial blood pressure averages vary from 203 to 219 mm Hg systolic and 97 to 104 mm Hg diastolic. T-waves are inverted in Leads I, II, and IV, they are biphasic in Lead III. There are no hemorrhages or exudates present in optic fundi, and papilledema is grade 2. Urine protein equals 0.3 gm per 24 hours, and hemoglobin is 66 per cent.

Approximately 12 shock-like reactions have occurred and occasional episodes of pain in back and chest have been experienced during the course of treatment.

Case 9 B T (730) This colored female, 46 years of age, discovered she had hypertension in 1938. Her complaints on admission were nocturia of many years' duration, headaches, fatigability, progressive loss of memory and eyesight, ringing in her ears, and on two occasions severe epistaxis.

On examination there were seen in the optic fundi grade 3 constriction and sclerosis of the retinal arterioles, grade 1 hemorrhages, and grade 1 papilledema. The heart was greatly enlarged, the mediastinum was widened, and a systolic murmur was heard at the cardiac apex and at the left sternal border in the second interspace. The liver was palpable 2.5 cm below the right costal margin. During the control period of observation she became decompensated and was digitalized.

Urea clearance was 42.7 per cent of average normal. Addis examination revealed a maximum specific gravity of 1.015. Transverse cardiac diameter was +35 per cent of normal. The electrocardiogram showed inverted T-waves in Leads I and IV and biphasic T-waves in Lead II. Blood Kline was 2+ and Kahn was 3+. Arterial blood pressure average was 241 mm Hg systolic and 130 mm diastolic for a week before kidney extract therapy was instituted. The arterial blood pressure average fell gradually to 209 mm Hg systolic and 106 mm diastolic. Kidney extract was discontinued for three weeks and the blood pressure rose to an average of 253 mm Hg systolic and 136 mm diastolic. Symptoms of mild decompensation appeared and headaches returned. Kidney extract therapy was resumed, and arterial blood pressure fell within two weeks to average 204 mm Hg systolic and 106 mm diastolic.

The patient was discharged from the hospital, is symptom free, and has resumed her household duties. Weekly arterial blood pressure averages vary from 224 to 243 mm Hg systolic and 113 to 130 mm Hg diastolic. The electrocardiogram now exhibits biphasic T-waves in Leads I and III and inverted T-waves in Leads II and IV. The optic fundi show grade 3 constriction and sclerosis of retinal arterioles, no hemorrhages, and a \pm papilledema. Urea clearance is 46.5 per cent average normal. Maximum urinary specific gravity is 1.016.

The patient has had three shock-like reactions and many episodes of cramping pain in chest and back following injections of kidney extract.

No		Hosp No 730 B.T.		46 yrs. ht 171 cm.		Weight		84 kg.					
MALIGNANT HYPERTENSION													
MONTHS		1 2 3 4 5 6 7 8 9 10											
BLOOD VESSELS	BLOOD PRESSURE												
		FINDUS CHANGES	Cor art										
			Scr art										
			Exudate										
			Ref hem										
Pop Edem													
KIDNEYS	UREA CLEARANCE % average normal												
	NON PROTEIN URINE SPECIFIC GRAVITY												
	HEMATURIA MILLIONS R.B.C./12 Hrs.												
	URINE PROTEIN Cn/24 Hrs.												
	BLOOD HEMOGLOBIN (HGWOMER) 15.6 Gm ± 100%												
	PLASMA PROTEINS Grams per 100 cc. TOTAL ALBUMIN												
HEART	EDEMA												
	TRANSVERSE CARDIAC DIAMETER % deviation from normal	+30 +20 +10 0											
	DYSPNEA												
	PULSE RATE												
	PRECORDIAL PAIN												
MISCELLANEOUS	BLUSHING												
	HEADACHE												
	EMOTIONAL INSTABILITY												
	VENOUS PRESSURE (cm of blood)												
	CIRCULATION TIME (saccharin arm to tongue)												
VITAL CAPACITY (% of Normal)													

No. D.H. Hosp. No. 742 w 38 yrs. h 5'5" cm. Weight 49 kg.

MALIGNANT HYPERTENSION

MONTHS

1 52 53 54 55 56 57 58 59 60

BLOOD VESSELS

BLOOD PRESSURE

FUNDUS CHANGES

Cor art
Scler art
Exudate
Ret hem
Pap Edem.

KIDNEYS

UREA CLEARANCE % average normal

NON PROTEIN URINE SPECIFIC GRAVITY

HEMATURIA MILLIONS R.B.C. /12 Hrs.

URINE PROTEIN Grams/24 Hrs.

BLOOD HEMOGLOBIN (in grams)

PLASMA PROTEINS Grams per 100 cc.

EDEMA

TRANSVERSE CARDIAC DIAMETER % deviation from normal

DYSPNEA

PULSE RATE

PALPITATION

PRE CORDIAL PAIN

MISCELLANEOUS

BLUSHING

HEADACHE

EMOTIONAL INSTABILITY

Venous Pressure cm. of blood

Circulation Time Saphenous

Vital Capacity % of Normal

MONTHS		1	2	3	6	8	9	10		
BLOOD VESSELS	BLOOD PRESSURE									
		FUNDUS CHANGES	Ctr art Scir art Exudate Ret hem Pap Edem							
KIDNEYS	UREA CLEARANCE % average normal									
	NON PROTEIN URINE SPECIFIC GRAVITY									
	HEMATURIA MILLIONS R.E.C./12 hrs.									
	URINE PROTEIN Gm/24 hrs.									
	BLOOD HEMOGLOBIN (H&COEM) 15 G Gm = 100%									
	PLASMA PROTEINS Grams per 100 cc.									
	EDEMA									
HEART	TRANSVERSE CARDIAC DIAMETER % deviation from normal									
	DYSPNEA									
	PULSE RATE									
	PAUPTATION									
MISCELLANEOUS	PRE-CORDIAL PAIN									
	BLUSHING									
	HEADACHE									
	EMOTIONAL INSTABILITY									
	Venous Pressure cm. of Blood									
	Circulation Time Ether %Mg SO.									
	Vital Capacity % of Normal									

Case 10 D H (742) A white female, 38 years of age, complained of hypertension known for five years, fatigability, palpitation, dyspnea, and excessive perspiration. Six months before admission she had two attacks of paroxysmal nocturnal dyspnea, disabling headaches with nausea and vomiting. Blood pressure was 232 mm Hg systolic and 130 mm diastolic. Ocular fundi revealed grade 2 constriction and grade 3 sclerosis of the retinal vessels, grade 1 papilledema and hemorrhages. The heart was enlarged in all diameters, especially to the left (+25 deviation). The second heart sound was reduplicated in all areas. There were râles at both lung bases. The liver edge was palpated $1\frac{1}{2}$ cm below the right costal margin.

Urea clearance was 70 per cent of average normal, maximal ability to concentrate urine was 1 018. Venous pressure was 22 cm of blood and circulation time 20 seconds (saccharin aim to tongue). Vital capacity was 80 per cent of average normal. The electrocardiogram showed left axis deviation and T-waves inverted in Leads I and II.

This patient was digitalized and kept at bed rest for three weeks. Arterial pressure averaged 238 mm Hg systolic and 128 mm diastolic. Symptoms of decompensation disappeared. Venous pressure fell to 15 cm of blood, and circulation time to 15 seconds. Kidney extract was begun at the end of the third week during bed rest. Arterial pressure fell to an average of 205 mm Hg systolic and 104 mm diastolic. Venous pressure became 7 cm of blood. Circulation time was 12 seconds. The hypertensive retinopathy improved to leave only grade 3 constriction and grade 2 sclerosis of the retinal vessels. All subjective symptoms disappeared.

Treatment extended over six months' time. She had chills and fever with urticaria on an average of once weekly, and two shock-like reactions. During the sixth month of treatment with intramuscular kidney extract she complained of joint pains. These followed kidney extract injections. Eosinophilia (8 per cent) was found and the skin was sensitive to 1:1,000 dilution of kidney extract. When kidney extract and digitalis were discontinued six days the blood pressure rose to a weekly average of 224 mm Hg systolic and 112 mm diastolic, and during one period of three days it reached 260 mm Hg systolic and 120 mm diastolic. Acute left ventricular failure supervened. Two small hemorrhages and grade 1 papilledema were seen in ocular fundi. Restoration of cardiac compensation, administration of kidney extract following rapid desensitization reduced the blood pressure to an average of 200 mm Hg systolic and 98 mm diastolic with only partial relief of joint pains. Abdominal pain replaced the joint pains, and was of such severity as to suggest intestinal obstruction. After partial decompression, tenderness localized over the right upper quadrant. An exploratory operation revealed that the gall-bladder was edematous and thickened. A number of enlarged lymph nodes was seen, and nodules were felt in the liver. Microscopic examination showed a quite typical picture of periarteritis nodosa.

Case 11 C H (766) A colored female, aged 35, complained of headaches and dizziness for eight months, hypertension known for six months, and blindness.

Average arterial blood pressure was 186 mm Hg systolic and 136 mm diastolic. Examination of the ocular fundi showed grade 4 constriction of the retinal arterioles, and grade 3 sclerosis. Both nerve heads were irregular in outline, swollen and paler than normal. The electrocardiogram displayed left axis deviation. Urea clearance was 100 per cent of average normal. Maximal ability to concentrate urine was 1 030.

The first weekly average arterial blood pressure at bed rest was 186 mm Hg systolic and 136 mm diastolic. Renal extract was administered intramuscularly. The blood pressure fell to an average level of 142 mm Hg systolic and 103 mm diastolic for four weeks. Headaches were diminished in severity but sight was not restored. Constriction of retinal arterioles was reduced to grade 2. Kidney extract was discontinued. The arterial blood pressure rose to average 168 mm Hg systolic and 118 mm diastolic in two weeks' time and headaches recurred.

No J.F.		Hosp No. 746 w 67		59 yrs		ht 5'10" cm		Weight 74 kg		
MALIGNANT HYPERTENSION										
MONTHS		<div> <div>1</div> <div>215</div> <div>216</div> <div>217</div> <div>220</div> <div>224</div> <div>227</div> <div>232</div> <div>235</div> <div>238</div> <div>245</div> <div>255</div> <div>267</div> </div>								
		<div> <div>280</div> <div>260</div> <div>240</div> <div>220</div> <div>200</div> <div>180</div> <div>160</div> <div>140</div> <div>120</div> <div>100</div> <div>80</div> </div>								
BLOOD VESSELS	BLOOD PRESSURE									
		FUNDUS CHANGES	<div> <div>Chr art</div> <div>Scl art</div> <div>Exudate</div> <div>Rat hem</div> <div>Pap Edem</div> </div>							
KIDNEYS	UREA CLEARANCE % average normal	<div> <div>120</div> <div>100</div> <div>80</div> <div>60</div> <div>40</div> <div>20</div> <div>10</div> <div>5</div> </div>								
	NON PROTEIN URINE SPECIFIC GRAVITY	<div> <div>1.035</div> <div>1.030</div> <div>1.025</div> <div>1.020</div> <div>1.015</div> <div>1.010</div> <div>1.005</div> <div>1.000</div> </div>								
	HEMATURIA MILLIONS # C/12 hrs	<div> <div>10</div> <div>5</div> <div>3</div> <div>1</div> <div>0.5</div> </div>								
	URINE PROTEIN Gm/24 hr.	<div> <div>10</div> <div>5</div> </div>								
	BLOOD HEMOGLOBIN (Hwcomet) 15.6 Gm % 100%	<div> <div>100</div> <div>90</div> <div>80</div> <div>70</div> <div>60</div> <div>50</div> <div>40</div> <div>30</div> <div>20</div> <div>10</div> </div>								
	PLASMA PROTEINS Grams per 100 cc. TOTAL ALBUMIN	<div> <div>9</div> <div>8</div> <div>7</div> <div>6</div> <div>5</div> <div>4</div> <div>3</div> <div>2</div> <div>1</div> </div>								
HEART	TRANSVERSE CARDIAC DIAMETER % deviation from normal	<div> <div>+30</div> <div>+20</div> <div>+10</div> <div>0</div> </div>								
	DYSPNEA	<div> <div>180</div> <div>140</div> <div>100</div> <div>60</div> </div>								
	PULSE RATE	<div> <div>180</div> <div>140</div> <div>100</div> <div>60</div> </div>								
	PAULPITATION	<div> <div>180</div> <div>140</div> <div>100</div> <div>60</div> </div>								
	PRE CORDIAL PAIN	<div> <div>180</div> <div>140</div> <div>100</div> <div>60</div> </div>								
MISCELLANEOUS	BLUSHING	<div> <div>180</div> <div>140</div> <div>100</div> <div>60</div> </div>								
	HEADACHE	<div> <div>180</div> <div>140</div> <div>100</div> <div>60</div> </div>								
	EMOTIONAL INSTABILITY	<div> <div>180</div> <div>140</div> <div>100</div> <div>60</div> </div>								
	Venous Pressure cm. of blood	<div> <div>20</div> <div>15</div> <div>10</div> <div>5</div> </div>								
	Circulation Time Saccharin	<div> <div>15</div> <div>10</div> <div>5</div> </div>								
Vital Capacity % of Normal		<div> <div>100</div> <div>80</div> <div>60</div> <div>40</div> <div>20</div> </div>								

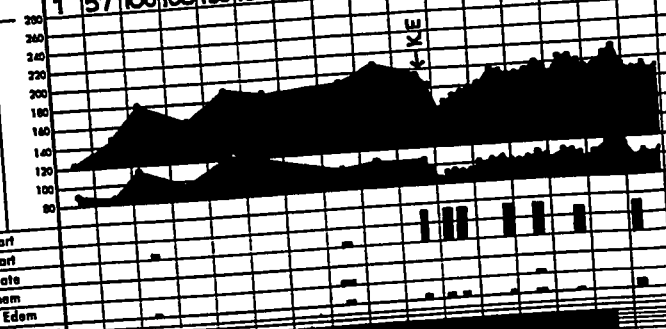
No C.L.B. Hosp No 750 wt 55 yrs. ht 162.5cm. Weight 772kg.

MALIGNANT HYPERTENSION

MONTHS 1 57 106 108 130 131 133 188 189 190 191 192 193 194 195 196

BLOOD VESSELS

BLOOD PRESSURE



FUNDUS CHANGES

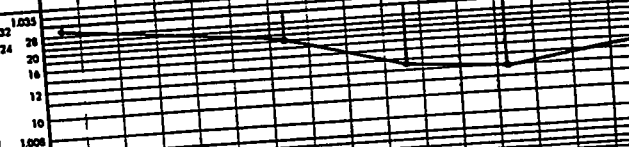


KIDNEYS

UREA CLEARANCE % average normal



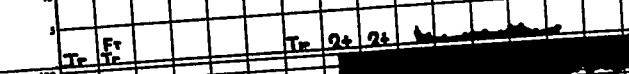
NON PROTEIN URINE SPECIFIC GRAVITY



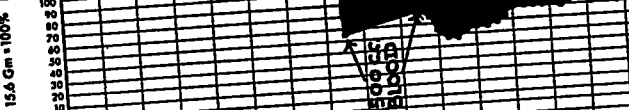
HEMATURIA MILLIONS R.B.C./12 hr.



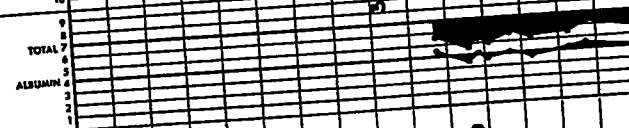
URINE PROTEIN Gm/24 hr.



BLOOD HEMOGLOBIN (HMCOR) 15.6 Gm % 100%



PLASMA PROTEINS Grams per 100 cc. TOTAL ALBUMIN



HEART

TRANSVERSE CARDIAC DIAMETER % deviation from normal



DYSPNEA



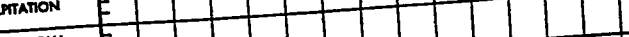
PULSE RATE



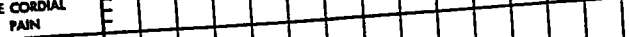
PALPITATION



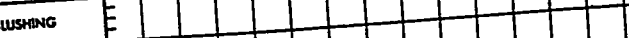
PRE CORDIAL PAIN



BLUSHING



HEADACHE

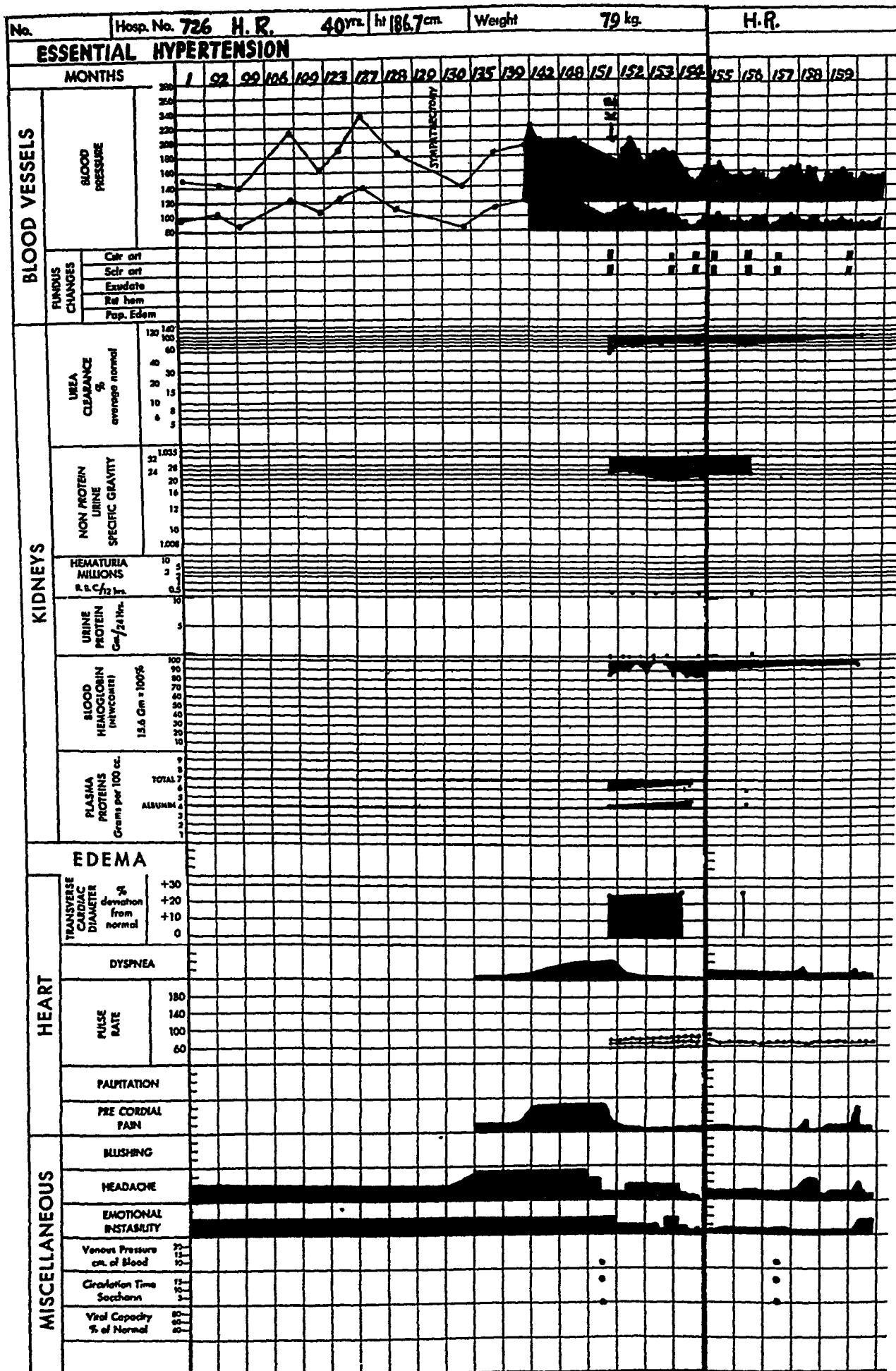


EMOTIONAL INSTABILITY



MISCELLANEOUS





Case 12 J F (746) This white male, aged 59 years, had hypertension of eight years' duration (190 to 270 mm Hg systolic and 100 to 170 mm Hg diastolic) Potassium thiocyanate was given in 1935 and the arterial pressure was reduced to an average of 164 mm Hg systolic and 100 mm diastolic The symptoms on admission were convulsive seizures with loss of consciousness, impaired memory and reasoning power The blood pressure was 236 mm Hg systolic and 150 mm diastolic The ocular fundi disclosed grade 3 constriction and sclerosis of retinal vessels, grade 1 hemorrhages, exudates, and papilledema The heart was enlarged to left, 11 cm from midline There were frequent extrasystoles A marked tremor in the outstretched hands was observed Urea clearance was 55 per cent of average normal Maximal ability to concentrate urine was 1015 Proteinuria amounted to 1 gm daily The electrocardiogram exhibited left axis deviation and inverted T-waves in Lead I

During bed rest the blood pressure averaged 225 mm Hg systolic and 136 mm diastolic Kidney extract was administered intramuscularly, the arterial pressure averaged 202 mm Hg systolic and 134 mm diastolic for first week of treatment and 192 mm Hg systolic and 120 mm diastolic for second week For three months of treatment arterial pressure averaged 210 mm Hg systolic and 118 mm diastolic

This course of therapy was attended with one shock-like reaction and six reactions with back and chest pain, chills, and fever The mental state cleared Retinal hemorrhages and exudates absorbed, papilledema regressed The T-waves in Lead I of the electrocardiogram became upright

ESSENTIAL HYPERTENSION

Case 13 C B (750) This 55-year-old white male complained of hypertension known for 20 years, headaches for five years that were relieved by bed rest and potassium thiocyanate, dependent edema of five years' duration, increasing nocturia, easy fatigability His blood hemoglobin was maintained at 65 to 70 per cent of average normal by virtue of seven 500 c c blood transfusions in a period of two months

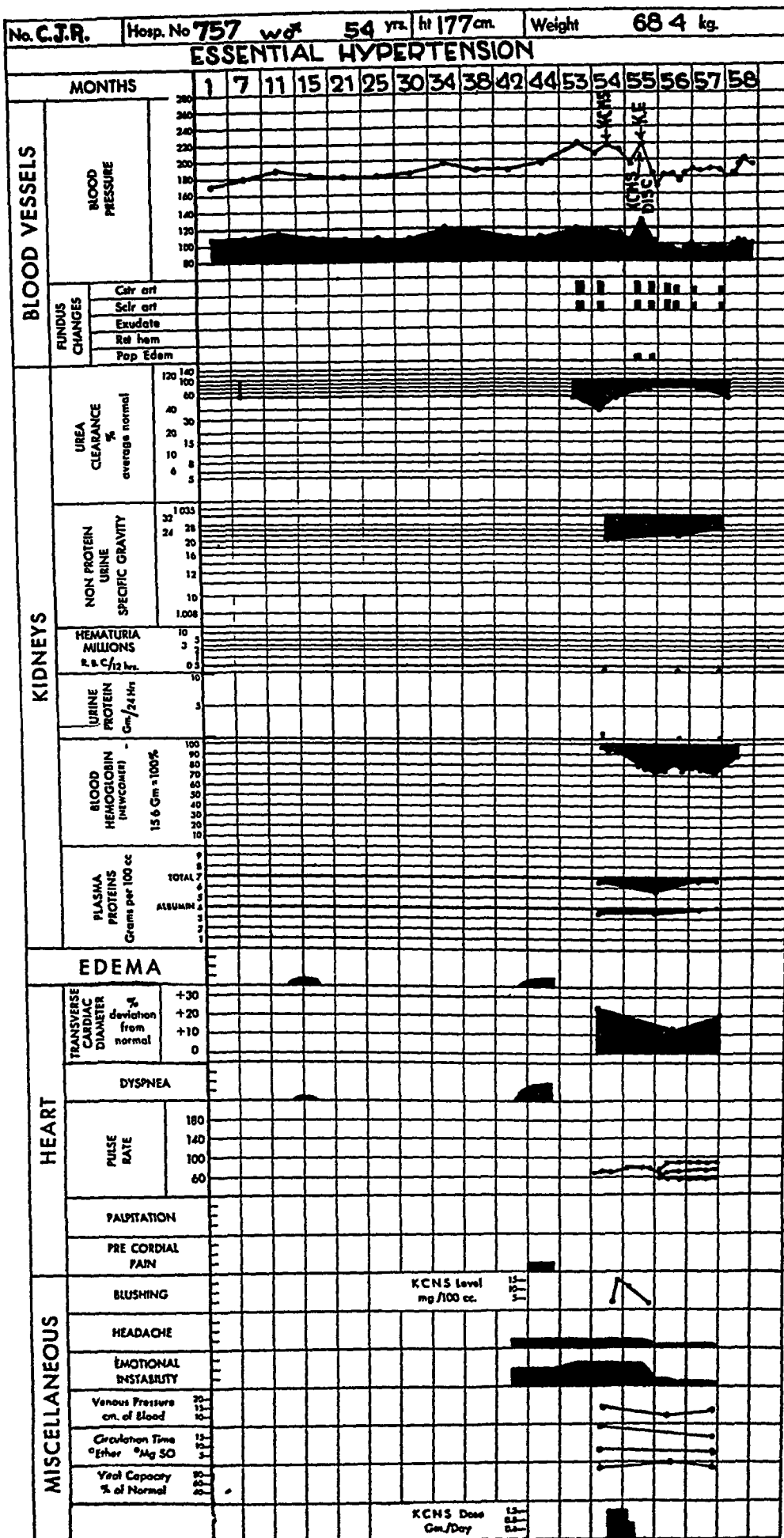
Physical findings were arterial pressure of 210 mm Hg systolic and 114 mm diastolic, grade 3 constriction and grade 4 sclerosis of the retinal arterioles, the heart was slightly enlarged in all diameters, there was grade 1 pitting edema of the lower extremities

Urea clearance was 28.4 per cent of average normal, maximal ability to concentrate urine was 10135, proteinuria amounted to 1.6 gm per 24 hours, plasma proteins were 5.74 gm per 100 c c

'Reticulogen' (Parenteral Liver Extract with Vitamin B₁, Lilly), ferrous sulfate, and daily doses of 'Multicebrin' failed to give a reticulocyte response or rise in blood hemoglobin Hemoglobin reached a low of 46 per cent of average normal without transfusions The blood pressure average for the first week in the hospital was 197 mm Hg systolic and 110 mm diastolic Kidney extract was administered intramuscularly After one week of therapy the blood pressure averaged 157 mm Hg systolic and 84 mm diastolic This low level was maintained for only four weeks During the following four months the pressure gradually rose to 190 to 200 mm Hg systolic and 95 to 105 mm Hg diastolic Blood hemoglobin rose without transfusion to an average of 77 per cent of normal Plasma proteins rose to 6.2 gm per 100 c c All symptoms, including dependent edema, have disappeared

This patient averaged a weekly bout of back and chest pain with chills and fever

Case 14 H R (726) A 40-year-old white male was observed to have hypertension in a routine physical examination four years ago He had had headaches for eight years, disabling anginal pain and dyspnea Rest and sedation, potassium thiocyanate, and bilateral splanchnic nerve resection gave no relief of symptoms or permanent fall in arterial blood pressure He came to Lilly Clinic in an ambulance after three months in bed



Blood pressure ranged from 170 to 205 mm Hg systolic and 110 to 120 diastolic. Ocular fundi revealed grade 2 constriction and grade 1 sclerosis of the retinal vessels. Heart was enlarged to 10.5 cm to left of midline. Urea clearance was 85 per cent of average normal, maximal ability to concentrate urine was 1.024. Electrocardiogram revealed left axis deviation.

Kidney extract given intramuscularly daily failed to lower blood pressure appreciably for seven weeks. At the end of this time, it began to fall and has been maintained at 140 to 158 mm Hg systolic and 80 to 98 mm Hg diastolic for six months. He has been treated as an out-patient for five months, leads a normal life, and is relatively free of symptoms.

He has had two shock-like reactions and four bouts of pain with chill and fever in seven months' time.

Case 15 C R (757) This 54-year-old white male was found five years ago to have hypertension (172 mm Hg systolic and 110 mm diastolic) by an insurance physician. His complaints have been increasing fatigue, headaches, extreme irritability, and personality change. He was treated with rest, potassium iodide, and sodium nitrite with no reduction in arterial pressure. He was treated intensively with potassium thiocyanate with no improvement.

Blood pressure averaged 220 mm Hg systolic and 120 mm diastolic. Arterioles in the ocular fundi showed grade 3 constriction, grade 2 sclerosis, and reddening of the optic discs. Chest film revealed cardiac hypertrophy to +25 per cent of average normal. Urea clearance was 80 per cent of average normal. Maximal ability to concentrate urine was 1.022. The electrocardiogram exhibited inverted T-waves in Leads I, II, and IV and left axis deviation.

At bed rest under potassium thiocyanate the blood pressure averaged 216 mm Hg systolic and 118 mm diastolic. Potassium thiocyanate was discontinued and after a suitable period kidney extract was administered intramuscularly, the blood pressure fell to an average of 172 mm Hg systolic and 96 mm diastolic during first week of treatment. It has remained between 170 to 190 systolic and 92 to 100 diastolic during three months of treatment. Constriction of retinal arterioles was reduced to grade 2. The symptoms have disappeared, and his former genial personality has returned.

During the course of treatment two shock-like reactions and four bouts of back and chest pain with chills and fever have occurred.

Case 16 A K (681) This white female, aged 46 years, complained of headaches, nervousness, pain over the heart, edema of the legs, and cramping in the feet and legs of a year's duration. Five years ago she passed through the menopause. Shortly before admission, vision in her left eye suddenly became blurred, and she was unable to see with her right eye.

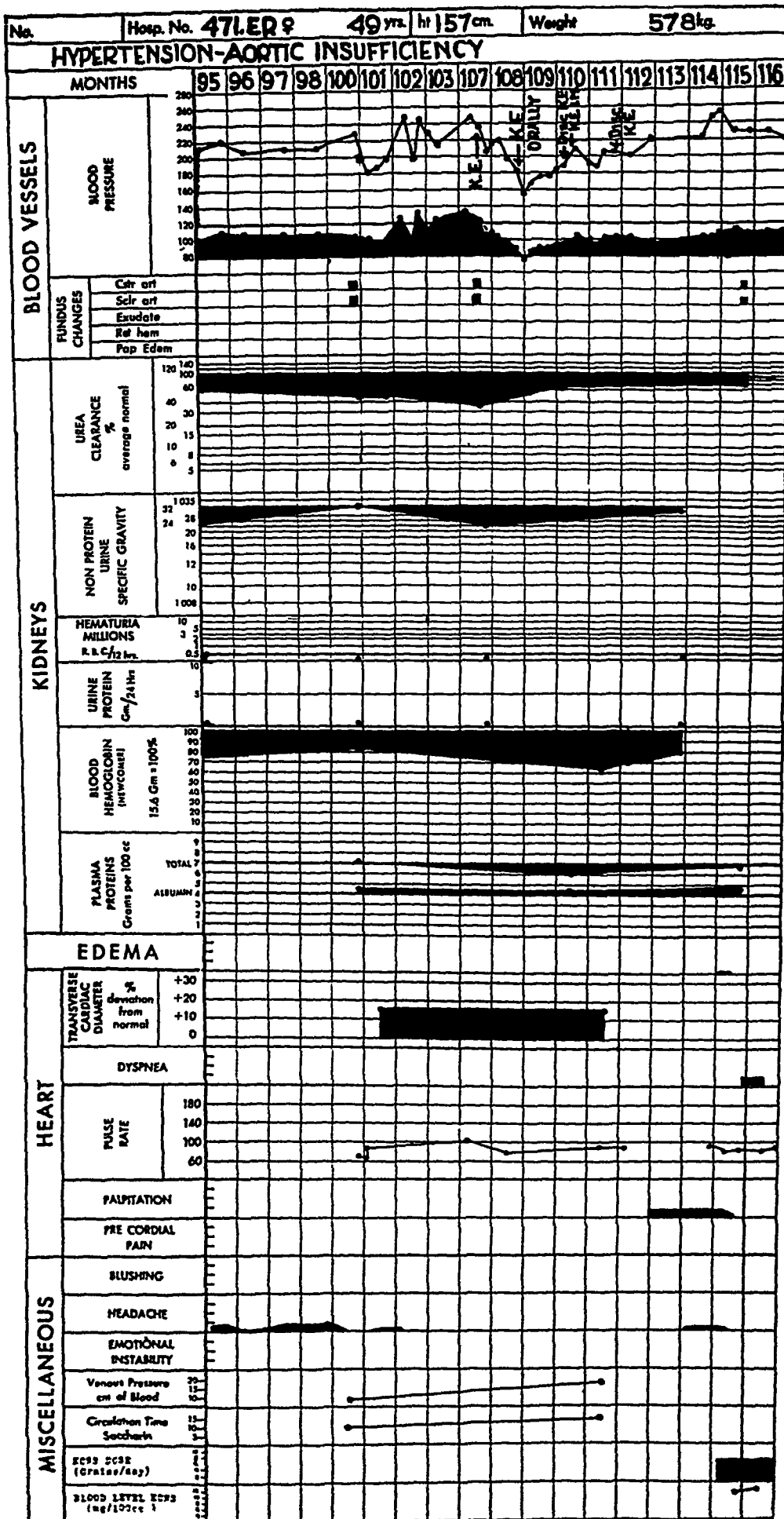
Physical examination revealed grade 2 constriction and sclerosis of the retinal arterioles. In the right retina there was a circular hemorrhagic area with a small patch of exudate. The heart was enlarged (+27 per cent deviation). Grade 1 edema was present over the ankles.

Urea clearance averaged 70 per cent of normal, and maximal ability to concentrate urine was 1.029. Some white blood cells were seen in the urine. A retrograde pyelogram revealed normal kidneys, urine culture was negative. The T-waves in Leads I, II, and III were inverted, and the S-T segment was depressed.

During the 16 day control period, the blood pressure averaged 237 mm Hg systolic and 130 mm diastolic. Renal extract was then administered, and during the next four days the average was 183 mm Hg systolic and 100 mm diastolic. A second extract was then employed for four days, and the blood pressure averaged 189 mm Hg systolic and 107 mm diastolic. The average while receiving a third extract was 189 mm Hg systolic and 109 mm diastolic. Still a fourth extract was used, and the average pressure was 189 mm Hg systolic and 102 mm diastolic. Extract was then discontinued, and the blood pressure rose to an average of 248 mm Hg systolic and 132 mm diastolic during a control period of 26 days.

No 681		Hosp No A K 8		46 yrs. ht 161.2 cm.		Weight		96 kg.						
ESSENTIAL HYPERTENSION														
MONTHS		1	2	3	4	5	6	7	8	9	10	11	15	
BLOOD VESSELS	BLOOD PRESSURE													
		FUNDUS CHANGES	Ctr art Scir art Exudate Ret hem Pap Edem											
KIDNEYS	UREA CLEARANCE % average normal													
	NON PROTEIN URINE SPECIFIC GRAVITY													
	HEMATURIA MILLIONS R & C /12 hr.													
	URINE PROTEIN Gm./24 Hr.													
	BLOOD HEMOGLOBIN (new count) 13.6 Gm. = 100%													
	PLASMA PROTEINS Grams per 100 cc.													
	EDEMA													
HEART	TRANSVERSE CARDIAC DIAMETER % deviation from normal													
	DYSPNEA													
	PULSE RATE													
	PALPITATION													
	PRE CORDIAL PAIN													
MISCELLANEOUS	BLUSHING													
	HEADACHE													
	EMOTIONAL INSTABILITY													
	Circulation Time Satchari													
	Venous Pressure cm. of Blood													
	Vital Capacity % of Normal													

Na JB		Hosp. No 724		c ♂ 37 yrs.		ht. 170 cm.		Weight		66 kg.		
<h2 style="text-align: center;">ESSENTIAL HYPERTENSION</h2>												
MONTHS		<div style="display: flex; justify-content: space-between;"> 121639464748495051525354 </div>										
BLOOD VESSELS	BLOOD PRESSURE											
		FUNDUS CHANGES	<div style="display: flex; justify-content: space-between;"> Curr. onScr. onExudateRet. hemPop. Edem. </div>									
KIDNEYS	UREA CLEARANCE % average normal											
	NON PROTEIN URINE SPECIFIC GRAVITY											
	HEMATURIA MILLIONS R.A.C. / 12 Hrs.											
	URINE PROTEIN Gm. / 24 Hrs.											
	BLOOD HEMOGLOBIN INTERCOMET 15 G. Gm. x 100%											
	PLASMA PROTEINS Grams per 100 cc											
EDEMA												
HEART	TRANSVERSE CARDIAC DIAMETER % deviation from normal											
	DYSPNEA											
	PULSE RATE											
	PALPITATION											
MISCELLANEOUS	PRE CORDIAL PAIN											
	BLUSHING											
	HEADACHE											
	EMOTIONAL INSTABILITY											
	Venous Pressure cm. of Blood											
	Circulation Time Saccharin											



Case 17 J B (724) This 37-year-old negro complained of occipital headaches for the past three years. Four years ago his blood pressure was normal, but two years ago it was 170 mm Hg systolic and 100 mm diastolic. Several members of his family are hypertensive.

On admission the blood pressure was 220 mm Hg systolic and 130 mm diastolic and, except for grade 1 constriction of the retinal arterioles, the physical examination was negative. Retrograde pyelograms showed no abnormalities. Electrocardiogram was normal, as were the other laboratory examinations. The cold pressor test caused the blood pressure to rise from 186 mm Hg systolic and 130 mm diastolic to 256 mm Hg systolic and 180 mm diastolic, and the 'Seconal' (Sodium propyl-methyl-carbinyl allyl barbiturate, Lilly) test caused a fall from 230 mm Hg systolic and 138 mm diastolic to 130 mm Hg systolic and 100 mm diastolic.

Renal extract was administered after the average pressure was established at 182 mm Hg systolic and 123 mm diastolic while the patient was in bed. After four days the patient was discharged from the clinic and received the injections daily as an out-patient. Since the patient was ambulant, the pressures would probably have been lower had he been confined to bed, as during the control period. The first week the average was reduced to 155 mm Hg systolic and 106 mm diastolic, the next week 160 mm Hg systolic and 107 mm diastolic, the third week 157 mm Hg systolic and 109 mm diastolic, and the fourth week 148 mm Hg systolic and 103 mm diastolic.

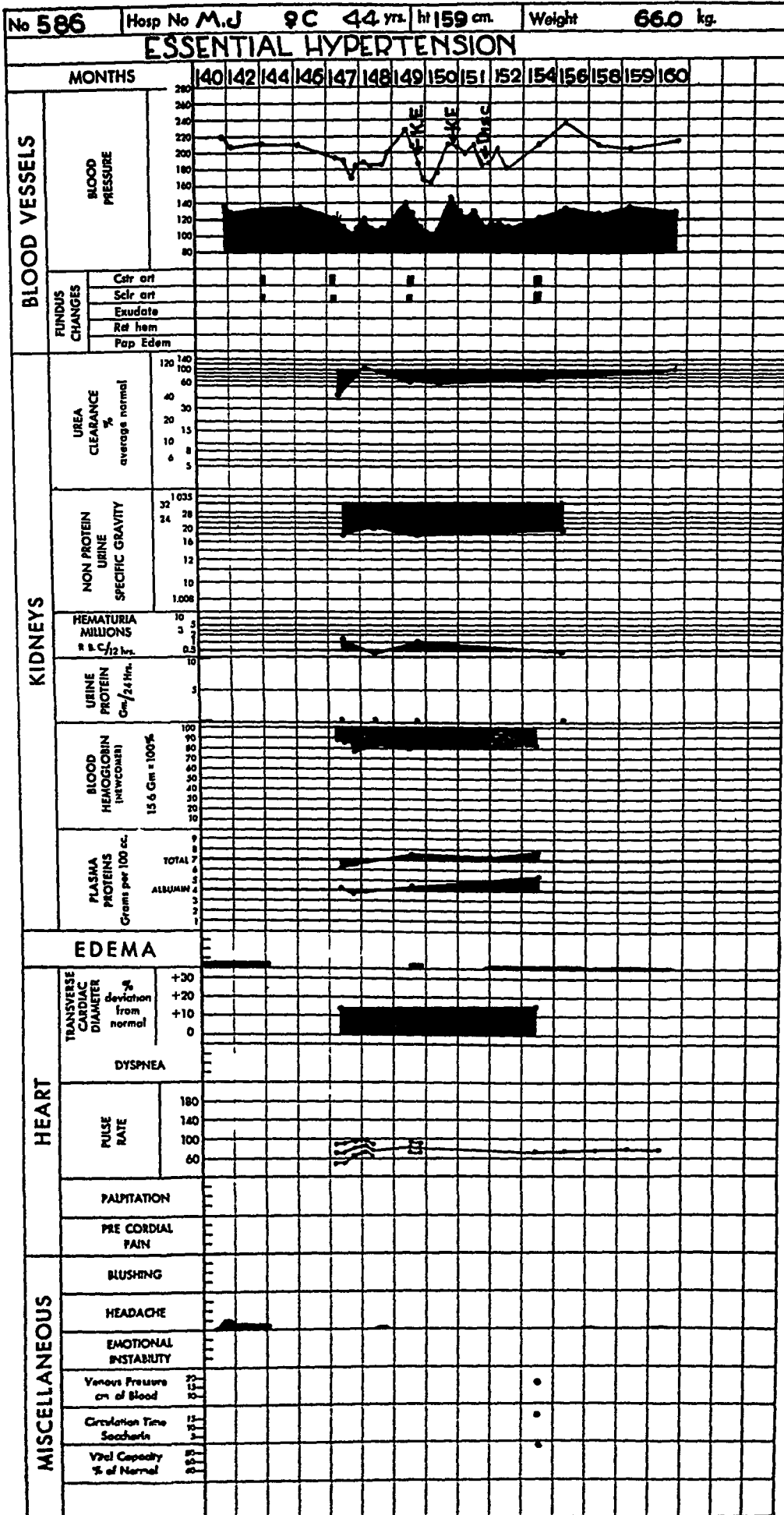
Arterial blood pressure was maintained at these levels for four months. He was symptom free and returned to work as a laborer. He had one shock-like reaction in this time. Kidney extract was discontinued for three weeks. Arterial blood pressure rose to an average of 171 mm Hg systolic and 119 mm diastolic. During this period he lost five pounds in body weight and headaches recurred. Kidney extract was administered, and arterial pressure was maintained at averages of 148 to 156 mm Hg systolic and 99 to 109 mm Hg diastolic.

Case 18 E P (741) This 49-year-old colored woman complained of headaches, dizziness, and dyspnea on exertion for the past seven years. Hypertension was found at that time. Since then the blood pressure has remained elevated, ranging from 200 to 270 mm Hg systolic and 120 to 180 mm Hg diastolic.

Physical examination showed grade 2 constriction and sclerosis of the retinal arteries. The heart was enlarged (+15 deviation), and there was a diastolic blow heard at the base. The electrocardiogram showed left axis deviation, slight inversion of the T-wave in Lead I, and an S-wave was present in Lead II. She is known to have had syphilis since 1935 and received sufficient treatment to alter the Wassermann reaction from positive to negative. The gold curve of the spinal fluid was that of paresis. Retrograde pyelograms were negative. The patient was treated in the out-patient clinic and was not confined to bed.

During the control period the blood pressure averaged 229 mm Hg systolic and 119 mm diastolic. The first two weeks after injection of kidney extract the pressure average was 196 mm Hg systolic and 98 mm diastolic, the following two weeks 182 mm Hg systolic and 90 mm diastolic, and the next week 157 mm Hg systolic and 78 mm diastolic. The site of the injection in the buttocks became swollen, and an abscess developed. Hence the extract was given, in five times the parenteral dosage by mouth. The blood pressure averages for each succeeding week were 168/85 mm Hg, 177/91 mm Hg, 178/91 mm Hg and 184/96 mm Hg. Extract was discontinued, and the average for the week was 210/104 mm Hg. For the next two weeks injections of extract were given at irregular intervals, and the blood pressure average was 186/92 mm Hg.

Case 19 M J (586) This patient, a colored female, aged 44 years, complained of headaches, vertigo, and dyspnea occasionally. Hypertension is believed to have occurred for the first time during her seventh pregnancy eleven years ago, and



eight years ago her blood pressure was found to be 150 mm Hg systolic and 88 mm diastolic. Three years ago it had risen to 200 mm Hg systolic and 140 mm diastolic.

On admission to the Lilly Clinic grade 2 constriction and grade 1 sclerosis of the retinal arteries were observed. The thyroid gland was diffusely enlarged (grade 1). The electrocardiogram showed left axis deviation. Urea clearance varied from 82 to 93 per cent of normal. Maximal ability to concentrate urine was 1 026. The Addis count was normal, as were the plasma proteins. The heart was slightly enlarged (+13 deviation). The retrograde pyelogram was normal except for slight dilatation of a calyx on the left side. The blood pressure during her stay of 50 days averaged 213 mm Hg systolic and 123 mm diastolic. As an out-patient the pressure average was 220 mm Hg systolic and 130 mm diastolic.

The patient was readmitted 10 months later. Sclerosis of the retinal arterioles was now graded 2 and constriction graded 3. The liver was palpable below the costal margin. The maximum ability to concentrate urine was reduced (1 018 to 1 021). Urea clearance was 103 per cent. The deviation from normal cardiac size was +15 per cent.

Blood pressure during the control period averaged 190 mm Hg systolic and 114 mm diastolic. The first kidney extract, given for a period of seven days, caused no significant fall in pressure (191 mm Hg systolic and 110 mm diastolic). The second extract, given for four days, was associated with a fall (170 mm Hg systolic and 106 mm diastolic average). Extract was discontinued, and the pressure rose to 200 mm Hg systolic and 114 mm diastolic.

The patient was again readmitted a month later. This time, during the control period of one week, the arterial pressure average was 210 mm Hg systolic and 125 mm diastolic. Renal extract was started, and for the next eight days the pressure fell to an average of 169 mm Hg systolic and 110 mm diastolic, at times being as low as 140 mm Hg systolic and 90 mm diastolic. During the next three weeks five different batches of extract were given. The blood pressure average was 175 mm Hg systolic and 99 mm diastolic, occasionally falling to low levels (132 mm Hg systolic and 84 mm diastolic). The patient felt well throughout the period she received extract, except for relatively slight pain around the site of the injections.

Extract was discontinued and the patient received treatment in the out-patient clinic. The blood pressure has varied between 204 and 236 mm Hg systolic and 120 and 140 mm Hg diastolic for 12 months.

CLINICAL RESULTS SUMMARIZED

1 *Effect on Arterial Pressure* At the outset it must be realized that in most patients the extracts have been prepared by varying methods. During the early part of our work it seemed desirable to employ only slight modifications of the standard ammonium sulfate fractional precipitation method. We determined also to employ only the parenteral method of administration for several reasons not the least of which was that Harrison, Grollman and Williams²⁶ are making an exact study of extracts when given by mouth. They were the first to show that their extract is effective when administered by this route.

Many variations have been introduced into our method for preparing renal extracts with the hope that greater purity would be achieved. The result has often been that the potency has been either reduced or lost.

Administration of renal extracts intramuscularly, daily, for a week or more is usually followed by only slight reduction in average blood pressure.

Continued administration leads to a progressive fall until normal or near normal levels are reached. If the extract is discontinued in most patients the pressure begins to rise within several days to a week. From our experience with the small group of 19 patients who have received prolonged treatment, our present opinion is that patients in whom the neurogenic component seems marked do not respond as quickly as do those in whom it is not so evident. Once the pressure is reduced it is maintained with smaller amounts of extract.

TABLE II

The Effect of Injection of Kidney Extract on T-Wave Changes, Dyspnea, Vital Capacity, Venous Pressure and Circulation Time

Malignant Hypertension

	Hosp No	T-Wave Changes		Circulation Time in Seconds Saccharin		Venous Pressure in cm Blood		Dyspnea	
		Before, Inverted in Leads	After Upright	Before	After	Before	After	Before	After
1	703	I, II	All leads	17	9	21	9	0	0
2	769	Not inverted	All leads	18	9	10.5	7.5	0	0
3	764	I, II, IV	All leads	13	11	7.75	11	++	0
4	671	I, II	All leads	7	9	7	9	+	0
5	662	I, II, IV	Unchanged	24	14	14	9	++++	++
6	553	Not inverted	All leads	33	21	15	17	+	+
7	683	Not inverted	All leads	—	—	5	—	+++	0
8	722	I, II, IV	Lead I	20	20	21	17	+	0
9	730	I, II, IV	II, III, IV	30	15	20	10	+	0
10	742	I, II	All leads	25	15	18	7.5	++	0
11	766	Not inverted	All leads	11	11	16.75	30	0	0
12	746	I	All leads	18	18	8.5	8.5	0	0
13	750	Not inverted	All leads	16	20	11	13½	+	+

Essential Hypertension

14	726	Not inverted	All leads	17	16	7	8.5	++	0
15	757	I, II, IV	Biphasic in I, II, IV	31	13	13	11.5	0	0
16	681	I, II, IV	II, III, IV	—	18	—	18	0	0
17	724	Not inverted	All leads	17	12	18	15	0	0
18	471	I	All leads	10	15	9	17	0	0
19	586	I, II, III	All leads	—	16	—	18	0	0

The length of time the patient has suffered from hypertension does not, within limits, appear to affect greatly the ease with which blood pressure is reduced. The arterial pressure of 2 of the 19 patients has been quite difficult to depress even moderately.

The diastolic pressure usually falls proportionately more than does the systolic pressure. It is not unusual to maintain the diastolic pressure in the range 80 to 110 mm Hg while the systolic is 160 to 200 mm Hg. This we interpret as being due to preëxisting arteriosclerosis, the typical hemodynamic picture of the latter appearing when that due to humorally produced hypertension is partially resolved.

Patients suffering from the malignant syndrome appear to respond well to administration of renal extract. The level of arterial pressure is no more difficult to depress than in some patients with benign hypertension. We wish, however, to emphasize that we make no pretense of presenting quantitative studies on the effectiveness of extracts in different types of hypertension.

2 Effect on the Heart The size of the heart, as estimated from measurement of the transverse cardiac diameter in roentgen-ray films, is reduced when the blood pressure is reduced. When the T-waves in Leads I and II were inverted they have been restored to their upright position (table 2). This has occurred in five patients with malignant hypertension and two with essential hypertension. One patient with terminal malignant hypertension and one with essential hypertension treated five weeks have shown no alteration. Circulation time as measured by injection of saccharin is somewhat decreased in some of the patients, especially when it has been grossly abnormal before treatment. Dyspnea has been lessened when present. It would be hazardous to state that the moderate but general improvement in cardiac function will be maintained on the basis of only a year and a half's experience. The continuity of this experience is, of course, marred from the clinical point of view by constant experimentation with new types of extract.

3 Effect on the Kidneys Urea clearance does not appear to be greatly influenced when the blood pressure falls as the result of kidney extract. This was not unexpected as Page²⁷ found no significant changes when the arterial pressure fell spontaneously in patients or was reduced by extensive sympathectomy or administration of potassium thiocyanate. In the six patients with essential hypertension studied by Corcoran and Page,¹⁹ there was a rise of renal blood flow of the order of 40 per cent in three, and half that amount in the others. Definite evidence of efferent arteriolar relaxation was found as measured by the fall of filtration fraction. The increase of flow in the nine patients with malignant hypertension was not as marked, averaging about 15 per cent, but the relaxation of the efferent arteriole was proportionately greater.

The ability of the kidneys to concentrate urine was determined by the specific gravity corrected for the protein content of the urine of a specimen taken in the last 12 hours of a 24 hour period without fluids (Addis test). Ten patients showed no significant change after several months of treatment. In five there has been a decline and in four an increase.

4 Ocular Changes The improvement of vision in patients with malignant hypertension is one of the most dramatic results of administration of kidney extract. Improvement may occur within several days or weeks.

Examination of the fundus shows that only moderate visible relaxation of the constricted arterioles occurs and almost no alteration in the visible changes interpreted by us as arteriolosclerosis. The disappearance of hemor-

TABLE III

Estimated Changes in Eyegrounds After Treatment with Kidney Extract

	Arterial Constriction		Sclerosis		Exudates		Hemorrhages		Papilledema	
	Before	After	Before	After	Before	After	Before	After	Before	After
<i>Malignant Hypertension</i>										
1	+	+	+	+	0	+	+	+	+	+
2	+	+	+	+	+	+	+	+	+	+
3	+	+	+	+	+	+	+	+	+	+
4	+	+	+	+	+	+	+	+	+	+
5	+	+	+	+	+	+	+	+	+	+
6	+	+	+	+	+	+	+	+	+	+
7	+	+	+	+	+	+	+	+	+	+
8	+	+	+	+	+	+	+	+	+	+
9	+	+	+	+	+	+	+	+	+	+
10	+	+	+	+	+	+	+	+	+	+
11	+	+	+	+	+	+	+	+	+	+
12	+	+	+	+	+	+	+	+	+	+
13	+	+	+	+	+	+	+	+	+	+
<i>Essential Hypertension</i>										
14	+	+	+	+	0	0	0	0	0	0
15	+	+	+	+	0	0	0	0	0	0
16	+	+	+	+	0	0	0	0	0	0
17	+	+	+	+	0	0	0	0	0	0
18	+	+	+	+	0	0	0	0	0	0
19	+	+	+	+	0	0	0	0	0	0

rhage, exudates and papilledema is the most marked and characteristic feature of the regressive changes occurring when extract is given

5 *Urine and Blood Changes* The number of red blood cells in the urine as ascertained by the Addis count is often sharply diminished after administration of kidney extract Profuse hematuria was unaffected in one patient with malignant hypertension who subsequently died Proteinuria may be reduced simultaneously with reduction in hematuria

TABLE IV

The Effect of Kidney Extract on the Number of Red Cells in the Urine, Proteinuria, Blood Hemoglobin and Plasma Proteins

		Addis Count in Urine				Hemoglobin in per cent		Plasma Proteins grams/100 c c	
		Hematuria millions RBC in 12 hrs		Proteinuria, Gm /24 hrs					
		Before	After	Before	After	Before	After	Before	After
<i>Malignant Hypertension</i>									
1	703	0 5	0 2	8 5	5 0	50	65	5 2	6 1
2	769	06	06	2	04	90	84 4	6 1	6 0
3	764	8	5	8	1	70	60	6 6	6 9
4	671	1 5	0 1	0 5	0 5	60	60	6 5	7 5
5	662	0 4	0 1	2 0	1 8	68	68	5 2	6 5
6	553	3 0—	0 6	0 5	0 1	90	70	6 5	6 5
7	683	2 0	10 0	3 0	1 0	70	58	6 3	4 5
8	722	0 6	0 3	3 0	0 5	65	65	7 60	7 5
9	730	0 21	0 28	2 5	37	80	61	6 65	6 56
10	742	0 2	0 2	0 2	0 2	80	80	6 20	7 2
11	766	0 3	0 3	0 3	0 3	82	66	6 15	6 69
12	746	0 2	0 5	0 7	0 5	85	85	6 67	6 67
13	750	0 1	0 1	1 5	1 0	50	77	5 0	6 2
<i>Essential Hypertension</i>									
14	726	0 4	0 2	0 142	1—	85	91	6 0	5 86
15	757	0 2	—	1 0	—	92	77	6 6	6 0
16	681	0 1—	0 1	0 1	0 1	90	90	7 3	7 7
17	724	0 1—	0 1	0 1	0 1	98	95	7 3	7 5
18	471	0 2—	0 15	0 5	0 5	82	80	7 0	6 5
19	586	1 0—	0 3	0 2	0 2	80	82	7 5	7 7

The change in hemoglobin in patients with malignant hypertension is of especial interest because during the usual course of events the loss is rapid and often indicates roughly the prognosis (see Page²⁸ for charts of typical untreated cases) After adequate treatment with extract the progressive fall is usually checked In two of nine patients rise has occurred Plasma proteins usually rise or are unchanged, the latter especially if they are already near the limits of normal

UNTOWARD REACTIONS TO KIDNEY EXTRACT

Two sorts of severe reactions to injection of renal extract are encountered. During the first, generalized flushing of the skin and lacrimation occur. The patient complains of a stinging sensation usually spreading from the face downwards. The blood pressure falls, dyspnea occurs and retrosternal pain or choking is felt. The patient is pale, perspiring, and the extremities are cold. The heart rate is slowed and abdominal cramps occur with passage of gas and stools. Edema of the face may appear. During such reactions adrenalin 1:10,000 solution is slowly administered. After termination of the reaction, fever lasting several hours occurs.

The second type of reaction is distinguished from the first especially by the fact that the blood pressure and pulse rate rise markedly rather than fall. The patient first complains of pain radiating from the site of injection up the back and down the legs. Spasm of the muscles, flushing and perspiration are observed. The reaction is over in from 3 to 7 minutes and is often relieved by injection intravenously of papaverine.

While these reactions are alarming, no after effects have occurred. The irregularity of the reactions is one of the most startling features. An extract which in sufficient dosage in most patients will elicit a reaction produces them only irregularly when the dose is reduced, but the same extract may, even in large doses, cause no reactions in some patients. In short, certain patients exhibit great resistance to reactions and even in the "reactors" their occurrence is erratic.

As purification has been carried farther, the incidence of reactions has been reduced but it still has to be reckoned with. For this reason, we have found it wise always to have an emergency tray containing 1:10,000 adrenalin in saline and ephedrin in syringes. If the adrenalin is administered at the very beginning of the reaction it may be all but avoided and so be the cause of only minor discomfort.

We have studied the records closely to ascertain whether any direct relationship exists between the occurrence of reactions and the fall in arterial pressure. For a day or more after a severe reaction the blood pressure may be, but is not necessarily, depressed. But depression of blood pressure occurs without reactions so it would be incorrect to attribute all or most of the depressor effects to reactions. In this connection it is of interest that reactions have never been observed in dogs or rats despite the fall in blood pressure.

The occurrence of these reactions shows that the preparation and administration of kidney extract are in the experimental stage. Effort is being made at the present time to purify the extracts sufficiently so that they will not occur.

DISCUSSION

Sufficient experimental evidence appears to demonstrate that arterial blood pressure can be reduced by parenteral administration of kidney extract in dogs and rats with renal hypertension and patients with essential and malignant hypertension. If administration of the extract is discontinued the blood pressure, after a variable length of time, rises.

The occurrence of reactions to the injection of extract in patients has been a disturbing side-effect, and they would not occur if given by mouth as recommended by Harrison, Grollman and Williams. We have not employed this method of administration because the latter workers are making a thorough study of it and because we believe a need might be found for a sufficiently pure extract for parenteral use. It would seem reasonable to suppose that reactions are due to sensitivity to foreign protein. Their highly irregular occurrence in so-called "reactor" patients lends no especial support to this view. Non-reactor patients are those in whom reactions are not induced by extracts which may cause sharp ones in the reactor type. It is of interest that there is a rough quantitative relationship between the amount of extract administered and the severity of the reaction. This suggests that the reactions are produced by impurities. There does not appear to be any direct relationship between the occurrence of reactions and the prolonged fall in blood pressure.

We have observed in human beings and in dogs that the amount of extract required initially to lower blood pressure varies, in some instances, markedly. When the fall begins it may progress rapidly, i.e. within three to five days in dogs, and in several weeks in patients. This suggests the possibility that before decline in arterial pressure may be expected, depleted reservoirs in the body must be filled, and it is only then that reduced arterial pressure results.

The observation of Corcoran and Page¹⁹ that angiotonin causes efferent arteriolar constriction with reduction of renal blood flow, which may be abolished by injection of kidney extracts, suggests some degree of specificity in the hypotensive action of these extracts. The pressor action of angiotonin as well is dampened or abolished. The evidence, we believe, is insufficient at present to determine the mechanism by which renal extracts reduce blood pressure.

Experience in the treatment of patients for the past year and a half suggests that the extracts might have merit. The yields of active material are low and the difficulty with reactions has been only partially overcome. It is therefore, not a practical treatment at the present time. Its use only in research clinics appears justified.

SUMMARY

1 A study has been made of the effects of parenteral injections of extracts of whole kidneys on 280 hypertensive dogs, 13 patients with malignant hypertension and 6 patients with essential hypertension. Some of the patients have been treated for about a year.

2 Arterial blood pressure has been significantly reduced and other objective as well as subjective signs of improvement have occurred sufficient to justify further experimentation in research clinics.

3 Because of occasional shock-like reactions and the lack of standard chemical procedures which yield a uniform product of high potency, it cannot at present be considered a practical treatment.

BIBLIOGRAPHY

- 1 TIGERSTEDT, R., and BERGMANN, P. G. Niere und Kreislauf, *Skand Arch f Physiol*, 1898, viii, 223
- 2 MERRILL, A., WILLIAMS, R. H., JR., and HARRISON, T. R. The effects of a pressor substance obtained from the kidneys on the renal circulation of rats and dogs, *Am Jr Med Sci*, 1938, cxcvi, 240
- 3 FASCILOLO, J. C., HOUSSAY, B. A., and TAQUINI, A. C. The blood pressure raising secretion of the ischemic kidney, *Jr Physiol*, 1938, xciv, 281
- 4 PAGE, I. H., and HELMER, O. M. Angiotonin-activator, renin and angiotonin inhibitor and the mechanism of angiotonin tachyphylaxis in normal, hypertensive and nephrectomized animals, *Jr Exper Med*, 1940, lxxi, 495
- 5 PAGE, I. H., and HELMER, O. M. A crystalline pressor substance, angiotonin, resulting from the reaction between renin and renin-activator, *Central Soc Clin Res*, 1939, xii, 17. Crystalline pressor substance (angiotonin) resulting from the reaction between renin and renin-activator, *Jr Exper Med*, 1940, lxxi, 29
- 6 BLALOCK, A., and LEVY, S. E. Studies of the etiology of renal hypertension, *Ann Surg*, 1937, cvi, 826
- 7 FASCILOLO, J. C. Acción del riñón sano sobre la hipertensión arterial por isquemia renal, *Rev Soc. argent de biol*, 1938, xiv, 15
- 8 KATZ, L. N., FRIEDMAN, M., ROBBARD, S., and WEINSTEIN, W. Observations on the genesis of renal hypertension, *Am Heart Jr*, 1939, xvii, 334
- 9 PAGE, I. H. On the nature of the pressor action of renin, *Jr Exper Med*, 1939, lxx, 521
- 10 FREEMAN, G. Anti-pressor effect of normal blood in experimental hypertension, *Proc Soc Exper Biol and Med*, 1940, xlv, 185
- 11 HARRISON, T. R., GROLLMAN, A., and WILLIAMS, J. R., JR. The antipressor action of renal extracts and their capacity to reduce the blood pressure of hypertensive rats, *Am Jr Physiol*, 1940, cxxviii, 716
- 12 PAGE, I. H., and HELMER, O. M. Unpublished observations
- 13 GROLLMAN, A., HARRISON, T. R., and WILLIAMS, J. R., JR. Humoral agents in the causation of hypertension, *Am Assoc Adv Sci*, Publication No 13, 1940, p 274
- 14 PAGE, I. H. Newer aspects of experimental hypertension, *Am Assoc Adv Sci*, Publication No 13, 1940, p 239
- 15 GROLLMAN, A., WILLIAMS, J. R., JR., and HARRISON, T. R. The preparation of renal extracts capable of reducing the blood pressure of animals with experimental renal hypertension, *Jr Biol Chem*, 1940, cxix, 115

- 16 PAGE, I H, HELMER, O M, KOHLSTAEDT, K G, FOUTS, P J, KEMPF, G F, and CORCORAN, A C *Substances in kidneys and muscle eliciting prolonged reduction of blood pressure in human and experimental hypertension*, *Proc Soc Exper Biol and Med*, 1940, xliii, 722
- 17 PAGE, I H, HELMER, O M, KOHLSTAEDT, K G, FOUTS, P J, and KEMPF, G F *Reduction of arterial blood pressure of hypertensive patients and animals with extracts of kidneys*, *Jr Exper Med*, 1941, lxxiii, 7
- 18 PAGE, I H *The production of persistent arterial hypertension by cellophane perinephritis*, *Jr Am Med Assoc*, 1939, cxiii, 2046
- 19 CORCORAN, A C, and PAGE, I H *Effects of renal extracts containing "angiotonin inhibitor" on renal blood flow and function in normal and hypertensive dogs and human beings*, *Am Jr Physiol*, 1941, cxxxiii, 248
- 20 CORCORAN, A C, and PAGE, I H *The effects of angiotonin on renal blood flow and glomerular filtration*, *Am Jr Physiol*, 1940, cxxx, 335
- 21 CORCORAN, A C, KOHLSTAEDT, K G, and PAGE, I H *Changes of arterial blood pressure and renal hemodynamics by injection of angiotonin in human beings*, *Proc Soc Exper Biol and Med*, 1941, xlv, 244
- 22 VAN SLYKE, D D, PAGE, I H, HILLER, A, and KIRK, E *Comparison of urea clearance calculated from the excretion of urea, of urea plus ammonia, and of nitrogen determinable by hypobromite*, *Jr Clin Invest.*, 1935, xiv, 901
- 23 ADDIS, T *The number of formed elements in the urinary sediment of normal individuals*, *Jr Clin Invest*, 1926, ii, 409
- 24 HOWE, P E *The determination of protein in blood by micromethod*, *Jr Biol Chem*, 1921, xlix, 109
- 25 CRANDALL, L A, JR, and ANDERSON, M X *Estimation of the state of hydration of the body by the amount of water available for the solution for sodium thiocyanate*, *Am Jr Digest Dis*, 1934, i, 1926
- 26 HARRISON, T R, GROLLMAN, A, and WILLIAMS, J R, JR *Reduction of elevated blood pressure by administration of renal extracts*, *Jr Am Med Assoc*, 1940, cxv, 1119
- 27 PAGE, I H *The effect on renal efficiency of lowering arterial blood pressure in cases of essential hypertension and nephritis*, *Jr Clin Invest*, 1934, xiii, 909
- 28 PAGE, I H *A clinical study of malignant hypertension*, *ANN INT MED*, 1939, xii, 978

RESULTS FROM THE MANAGEMENT OF BLEEDING GASTRIC AND DUODENAL ULCER *

By T GRIER MILLER, M D , F A C P , *Philadelphia, Pennsylvania*

THE purpose of this presentation is to direct attention to a dramatic improvement in some of the recently reported results from the treatment of profusely bleeding gastric and duodenal ulcer. This has followed the application to that emergency of a principle already well established in the management of uncomplicated ulcer—that of prompt, frequent and reasonably adequate feeding. Designed originally by Lenhartz and by Sippy to control the restlessness and the acidity of the empty stomach and so promote simple ulcer healing, the therapy based on this principle also tends, in the bleeding case, to stop the hemorrhage and, when combined with a sufficient fluid intake, to prevent or combat shock. As now employed in ulcer hemorrhage it consists primarily in the oral administration, beginning as soon as the patient comes under observation, even if still bleeding, and at frequent intervals thereafter, of an ample supply of non-irritating food and of fluid; secondarily, and varying with the inclination of the physician, it may include the use of alkalis, of hematinics, of sedatives and of transfusions. A measure of its practical value lies in the available statistics which indicate that the death rate from bleeding ulcer on the prompt feeding program has dropped to about one third what it was on the older and more commonly used starvation regimen.

The literature on the results obtained by the previously accepted method of medical management, that of immobilization, morphine and starvation during and for several days after the cessation of hemorrhage, gives an average mortality rate, for 5843 collected cases, of 87 per cent,¹ for some series as high as 25 per cent.² Even in the Scandinavian countries, where most cases even with minor hemorrhage are hospitalized, it has ranged from 7 to 10 per cent. Furthermore, one finds that the most favorable report on the surgical management of bleeding ulcer, that of Finsterer,³ gives a mortality rate of 6 per cent, others as high as 100 per cent, the average for 383 collected cases has been reported as 28 per cent.¹ One, of course, admits that many of the patients were operated upon only after all hope of cure by medical measures had passed, but that was not true of Finsterer's series. On the other hand, a complete review of the literature shows that for approximately 1400 cases of massive hemorrhage from ulcer, treated by prompt and adequate feeding, the gross mortality rate is only 3 per cent.⁴

Meulengracht⁵ very properly is given credit for the development of the prompt feeding program for hemorrhage, but six years previously Andre-

* Read at the Boston meeting of the American College of Physicians, April 21, 1941

From the Gastro-Intestinal Section (Kinsey-Thomas Foundation) of the Medical Clinic, University of Pennsylvania Hospital

sen,⁶ a Fellow of this College, outlined and recommended, on the basis of the same physiological principles and personal observations, that the administration of a solution of gelatin, orange or grape juice and lactose be started immediately after the cessation of the hemorrhage. Unfortunately he presented no results from that type of therapy, but in 1939 he⁷ did report on a series of 120 severely bleeding cases, having employed in them milk and cream in addition to his gelatin mixture and having started the feedings in the midst of the hemorrhage, the mortality rate in that series was 5 per cent.

It was only eight years ago that Meulengracht⁵ made his first report on this type of management, having had a mortality of 1.8 per cent in 109 cases. Later, in 1939, his gross mortality for 491 severely bleeding cases was 2 per cent.⁸ His program provides for the feeding of the patient from the onset of his hemorrhage and gives him, in six feedings, along with alkalies and iron, a full and well balanced diet, including milk, cereals, eggs, sliced and ground meats, cheese, mashed potatoes, pureed green vegetables, white bread, stewed fruits, tea and cocoa. He evolved the technic as a result of his observations, amply confirmed by other clinicians, that exhausted patients often die of gastric hemorrhage in spite of scrupulous dieting, that some patients with protracted hemorrhage do not stop bleeding until fed and that some patients with profuse hemorrhage and without special variation in their diet recover, also, of his personal conviction that peptic ulcer healing is not promoted by starvation, a stomach empty but for its own acid secretion or a diet deficient in calories and vitamins.

Witts,⁹ of St. Bartholomew's, in reporting in 1937 on 27 cases of bleeding from the stomach and duodenum treated by prompt feeding, ably presented additional arguments in favor of that type of management and emphasized the importance at the same time of an adequate intake of fluid. He especially referred to the significance of Blalock's¹⁰ experimental work on post-hemorrhagic shock in this connection and pointed out that death in the profusely bleeding cases results more often from shock than from exsanguination. He also called attention to the work of Cullinan and Price,¹¹ which showed that gastric hemorrhage is more likely to occur after starvation, and to the belief of Hunter that a free flow of saliva assists in clot formation. Subsequently Jones,¹² from Witts' clinic, reported on 50 bleeding ulcer cases, including those in the original series and all treated by prompt feeding, with but one death, that of a 69-year-old woman who had in addition a severe erosive gastritis. The treatment was the same as Meulengracht's except that the food was more liquid, totalled about 2750 c.c. per day and included 2500 to 3500 calories, also a plentiful supply of vitamins. No alkalies or other drugs were allowed, and transfusions were reserved for obvious shock.

More recently Woldman,¹³ who developed the method of treating uncomplicated gastric and duodenal ulcer by a continuous intragastric drip of a solution of aluminum hydroxide, has applied that method together with

second-hour bland feedings in the management of massive bleeding from ulcer. He lost only three cases out of a total of 144 (2.1 per cent), and attributes his results entirely to the neutralization of the acid gastric juice by the aluminum preparation. Since, however, his results are no better than those obtained by the use of the prompt feeding program alone, which he also employed, one must await further comparative studies as to the influence of the aluminum hydroxide. Lineberry and Issos¹⁴ got even better results, with no mortality, in a series of 36 cases treated by the formal Sippy regimen begun in the midst of the hemorrhage.

My personal experience with the prompt and adequate feeding program for massive hemorrhage from gastric and duodenal ulcer has been limited to 32 cases, which are being reported separately by Nicholson and Miller.⁴ Of these but one patient died—a man who subsequently was found to have had at the same time a duodenal perforation. The average hemoglobin reading for the series was 44 per cent. Twelve of the patients, before being seen by one of our staff members, had been starved and given morphine, but otherwise all of them, on admission to the hospital, were promptly put on six feedings a day of an ample smooth diet, usually without meat for the first 24 hours, and given only sodium phenobarbital as a sedative, no alkalis or iron. A blood transfusion was given to 11 subjects. In some of the cases the bleeding apparently had stopped before the feeding was begun, in others it ceased quite promptly, in still others it persisted for several days, in one for a week and yet without the development of shock.

As one reviews the various reports he is impressed by the fact that some of the cases were hopeless from the beginning. Autopsy often revealed a large eroded artery, and in many of them the artery was in the base of an old calloused ulcer which tended to prevent its closure. Some were hospitalized late in the hemorrhage when almost exsanguinated and died before any form of treatment could be given a trial, this was true of four of the 10 fatal cases in Meulengracht's series. All of these, however, have been included in the quoted mortality figures. If all the fatal cases that were practically exsanguinated and moribund before the treatment was inaugurated, those with perforation, like our own, Jones' single fatal case with extensive erosive gastritis and three of Andresen's cases, which he believed died as a result of excessive transfusions, are eliminated, the mortality from the feeding program is reduced to slightly less than 2 per cent.⁴

In view of such a low mortality rate from the medical management of bleeding ulcer one naturally wonders if surgical interference is ever justified. It is appreciated that if one could judge accurately from the beginning what patients would not recover on a medical program, an occasional one of them might be saved by prompt surgery. Such a selection, however, is obviously impossible, and if any one of those, who otherwise would have recovered, should be operated upon he is subjected to a fair chance of losing his life. This consideration, together with the fact, as pointed out by Witts, that the

best individual medical results are far superior to the best individual surgical results for any group of patients, leads me to believe that none of them in the midst of the hemorrhage, unless an additional complication such as perforation is diagnosed, should be managed surgically

Although the reduction in the mortality rate is the most convincing factor in favor of the prompt and adequate feeding regimen for bleeding gastric and duodenal ulcer, everyone who has written on the subject has been equally impressed by its effects on the morale of the patient. Instead of being restless, agitated and frightened, he is calm, composed, comfortable and co-operative. Nausea rarely persists after beginning the feedings, and usually, if the treatment is begun early in the hemorrhage, the feeling of exhaustion, that formerly was provoked or at least maintained by his thirst, hunger and enforced immobility, is absent. Morphine usually is not required, and this in itself tends to maintain a more tonic condition of the gastric and duodenal musculature.¹⁵ The patient, according to Witts, looks, feels and does well.

This brief review of some of the recent reports on the medical management of bleeding gastric and duodenal ulcer indicates (1) that far better results, both as regards the survival of the patient and his comfort, may be expected from a prompt and adequate feeding regimen, including plenty of fluid, than from the better known starvation program, (2) that the particular type of diet administered, so long as it is non-irritating, is of less importance than that it be given promptly and in adequate amount, and (3) that surgical intervention in the midst of the hemorrhage is rarely, if ever, justified.

REFERENCES

- 1 MILLER, T G, and ELSOM, K A. The management of massive hemorrhage from peptic ulcer, *Med Clin N Am*, 1938, xxii, 1711
- 2 CHIESMAN, W E. Mortality of severe hemorrhage from peptic ulcers, *Lancet*, 1932, ii, 722
- 3 FINSTERER, H. Operative treatment of severe gastric hemorrhage of ulcer origin, *Lancet*, 1936, ii, 303
- 4 NICHOLSON, J T L, and MILLER, T G. The prompt-feeding program for bleeding gastric and duodenal ulcer: a report on 32 cases and an analysis of 1396 cases (In press)
- 5 MEULENGRACHT, E. Treatment of hematemesis and melena, *Proceedings of 16th Scandinavian Congress for Internal Medicine*, 1933, *Arch Med Scand Supp*, 1934, lix, 375
- 6 ANDRESEN, A F R. The treatment of gastric hemorrhage, *Jr Am Med Assoc*, 1927, lxxxix, 1397
- 7 ANDRESEN, A F R. Results of treatment of massive gastric hemorrhage, *Am Jr Digest Dis*, 1939, vi, 641
- 8 MEULENGRACHT, E. Medical treatment of peptic ulcer and its complications, *Brit. Med Jr*, 1939, ii, 321
- 9 WITTS, L J. Hematemesis and melena, *Brit Med Jr*, 1937, i, 847
- 10 BLALOCK, A. Trauma, occupational diseases and hazards, shock and hemorrhage, *Bull N Y Acad Med*, 1936, xii, 610

- 11 CULLINAN, E R, and PRICE, R K Hematemesis following peptic ulceration, prognosis and treatment, St Barth Hosp Rep, 1932, lxxv, 185
- 12 JONES, F A Hematemesis and melena Observations on the use of continuous drip transfusions, Brit Med Jr, 1939, i, 915
- 13 WOLDMAN, E E The treatment of massive gastroduodenal hemorrhage by the continuous administration of colloidal aluminum hydroxide, Am Jr Digest Dis, 1941, viii, 39
- 14 LINEBERRY, E D, and ISSOS, D N Treatment of massive hemorrhage from duodenal or gastric ulcer, South Med Jr, 1937, xxx, 1228
- 15 ABBOTT, W O, and PENDERGRASS, E P Intubation studies of the human small intestine V The motor effects of single clinical doses of morphine sulphate in normal subjects, Am Jr Roentgenol, 1936, xxxv, 289

WEIL'S DISEASE; REPORT OF SIX CASES *

By HOWARD K RATHBUN and JULIUS M WAGHELSTEIN,
Baltimore, Maryland

WEIL,¹ in 1886, described a disease characterized by jaundice and nephritis. Inada and his co-workers² in a remarkable series of reports delineated the clinical and pathological picture, described the etiological agent and named it *Spirochaeta icterohaemorrhagica*. Noguchi,³ in 1917, reported the presence in American wild rats of a spirochete morphologically and immunologically identical with the Japanese and European strains. In 1918 he⁴ further described the organism and called it *Leptospira icterohaemorrhagica*. Wadsworth et al⁵ described the first case in the United States which occurred as an accidental infection in a laboratory worker.

Noguchi⁴ described the causative organism as a very tightly and regularly wound cylindrical filament tapering to sharply pointed ends. It usually assumes a graceful hook at one or both ends. The main portion is straight or slightly bent. The length of the organism varies from 3 to 40 micra. The distance between the apices of the adjacent spirals is 0.5 micron. There are about six spirals in each terminal portion. In the dark-field the organism is seen to be dotted with alternate bright and shadowy portions surrounded by a halo. The leptospira proceeds by a rotary motion and appears to be propelled from the rear by a rotating hook. The organism passes through a Berkefeld filter. Unlike other spirochetes it resists the destructive action of 10 per cent saponin. Schuffner in 1934⁶ reported the isolation, from dogs and from one case in a human, of a morphologically similar but immunologically and epidemiologically somewhat different strain of leptospirae which he called *Leptospira camicola*. Several human cases due to this strain have since been reported.

It has been known for some time that the rat is the animal host and that the leptospirae are harbored in the animal's kidneys and excreted in the urine^{2, 3, 7, 8, 9, 10}. Human infection usually results from contact with the infected urine, although it may rarely occur as a result of the bite of a rat^{26, 27}. The disease has been found to occur most frequently in sewer workers,¹¹ miners,²⁷ workers in rice fields,^{2a} fish-workers,^{12, 13, 14} and other occupations involving close contact with the urine of infected rats. Such contact takes place in a wet or damp environment. It also occurs following swimming or near drowning in contaminated water. A number of cases occur in which no clearcut history of such contact may be obtained.

The guinea-pig has been found to be very easily infected and therefore a satisfactory animal for experimental study of the disease. Small guinea-pigs

* Received for publication June 25, 1941

From the Medical Service of the Baltimore City Hospitals, Baltimore, Maryland

(100 to 150 grams) should be used Packchamian¹⁵ found that certain species of American deer mice are also suitable animals but the ordinary laboratory white mice as well as rats may be carriers of the organism The guinea-pig is rarely found to be spontaneously infected Inada et al²⁰ stated that the leptospirae could pass through either the healthy or the abraded skin of guinea-pigs Since in some of their patients local glandular enlargement was present, they concluded that the skin may sometimes be the point of entrance of the organism Schuffner,⁸ however, found that guinea-pigs could be infected by prolonged immersion in contaminated water only if their skins were scarified He also found that the disease was considerably more frequent in humans who nearly drowned than in swimmers He concluded that this was probably due to contact of the water with the bronchial and intestinal epithelium Jorge¹⁶ reported an epidemic arising from drinking water

Inada²⁰ divided the disease into three stages This division is of practical importance since the laboratory procedures necessary in establishing the diagnosis give different results in the three stages The first, or febrile stage is preceded by an incubation period varying between 4 and 19 days, usually between 7 and 13 days During the first stage the leptospirae are circulating in the blood There are no demonstrable antibodies in the blood at this time The organism may be in the urine The disease varies widely in its severity There may be a severe chill followed by a high fever and headache Chill is not always present, but, though the disease be mild or severe, the onset is usually sudden Restlessness, apathy, delirium, or coma may be present Muscular pains and tenderness are common and may be cramp-like and are most frequent in the thighs, back and calves, but may be in the abdominal wall and cause considerable confusion with acute intra-abdominal conditions Anorexia, nausea, vomiting or diarrhea may occur Prostration is frequently marked and may be out of proportion to the rest of the symptoms Cough or hiccough may be present Hyperemia of the conjunctivae is a common finding The tongue may be red or thickly coated There may be ulcers on it and on the mucous membranes of the mouth The tonsils may be red and swollen In an occasional case there is meningeal irritation The white blood count is elevated and usually is less than 20,000 per cubic millimeter Albumin, cells and casts are found in the urine at this time The first stage lasts from four to seven days

The first stage merges into the second, icteric, or toxic stage which lasts until the twelfth or thirteenth day By this time the leptospirae have usually disappeared from the blood but can be found in increasing numbers in the urine Immune bodies appear during this stage The symptoms of the first stage decrease in intensity Icterus and hemorrhagic phenomena consisting of epistaxes, hemoptyses, hematemeses, purpura and blood in the stools reach their greatest intensity General weakness, nervous symptoms and signs of cardiac weakness which have their onset during the middle or end of the first stage become most marked It should be stressed that icterus

occurs only in about one half of the cases. The temperature falls by lysis. Renal changes manifested by albuminuria, casts, red and white cells in the urine, oliguria or even anuria and a rising nonprotein nitrogen may be present according to the severity of the case. When death occurs it usually does so during the second stage due to toxemia, cardiac or renal insufficiency or a combination of these conditions.

In the third or convalescent stage organisms are not present in the blood but are in the urine. They have been demonstrated in the urine as long as seven or eight weeks after the onset of the disease. Antibodies develop fully during this period. Symptoms gradually subside and moderate to marked anemia and emaciation may then become apparent. Convalescence may be prolonged for several months. A second or "after fever," lasting from four to 20 days and occurring in 25 to 75 per cent of the cases, starts usually during the third week of the disease. The after fever is, in most cases, unassociated with other symptoms. The temperature may, however, be above that of the first stage.²⁹ It may recur three or four times in the same patient. *Leptospirae* have not been demonstrated in the blood during the after fever.

Walch-Sorgdrager¹⁷ emphasized the meningeal involvement occurring in the disease. Meningismus or meningitis may occur during the course of the more or less classical form of the disease or as a relatively isolated syndrome. Changes in the spinal fluid, such as increased protein content and pleocytosis, may occur in the typical cases of leptospiral infection without clinically demonstrable evidence of meningeal irritation, as well as in those cases with clinical meningitis. *Leptospirae* occasionally are found in the spinal fluid and may remain there for a longer period than they usually are present in the blood.¹⁸ Mortensen¹⁹ described a case complicated by meningitis and a complete paralysis of the lower extremities. He was able to collect three similar cases from the literature. He emphasized the fact that there may also be a parenchymal involvement of the nervous system in Weil's disease.

There may be an associated iritis or iridocyclitis which occurs in 10 to 44 per cent of the cases. This complication may appear between the sixteenth and forty-second day and may be associated with the after fever. Skin eruptions occur in 10 to 36 per cent of the cases. The rash may be morbilliform or scarlatiniform, may be large patches or maculopapules, may be erythematous, urticarial or hemorrhagic.¹⁷

The *leptospirae* have been found in practically every organ of the body.²⁰ The predominant pathological finding aside from the necrosis of the liver cells and nephritis, is hemorrhage due to capillary damage.²⁰ This is thought to be due to a local toxic effect upon the walls of the vessels. The organs are usually deeply bile stained.

The liver is normal in size or slightly enlarged. Of fairly common occurrence are the proliferation of hepatic cells and traces of bile stasis in the center of the liver lobule. The hepatic cells show active division, the nuclei are swollen and there may be two or three nuclei in some of the cells. In

some cases there may be focal necroses within the liver. Two factors probably play a part in the production of jaundice. one, the swelling of the cells and accompanying edema which may produce obstruction of the bile canaliculi, and two, the deleterious effect upon the liver cells by the leptospiral "toxin". The bile stasis is usually found in moderate degree in the central portion of the liver lobule and not in the periphery of the lobule or in the interlobular or larger ducts.

The kidneys are often enlarged and there may be swelling and more or less necrosis of the epithelium of the convoluted tubules. There may also be infiltration into the interstitial tissues chiefly of lymphocytes with some polymorphonuclear cells and eosinophiles. Small hemorrhages throughout may be noted.

The muscles most severely involved are those of the calf; others may also be affected. Macroscopically, punctate hemorrhages may be seen. Microscopically, the process characteristically selects parts of isolated fibers. With more extensive involvement adjacent fibers or even a whole field may be concerned. The pathological process consists of vacuolation, swelling, loss of striations, hyalinization and infiltration of the fibers with macrophages, polymorphonuclear and plasma cells. The substance of the fiber may be broken up into large lumps of hyaline material.

Kaneko and Okuda²⁸ studied the distribution of the leptospirae within the body. They found that early in the disease the organism is located extracellularly. With the progress of the disease and the development of immune bodies, the leptospirae tend to become more frequently enclosed within the cells and to disappear from organs other than the kidney. In the kidney they are found, early in the disease, in the trabeculae, tissue spaces and interstitial tissues, later, in the tubules.

Since the organisms are present in the blood during the first week and occasionally as late as the ninth day, they may be demonstrated there by dark-field examination or guinea-pig inoculation. Demonstration of the leptospirae in a dark-field preparation of blood is rather difficult. This is probably best accomplished by centrifuging the blood at low speeds and examining the plasma.⁶ Inada²⁹ stated that spirochetes appear in small numbers in the urine during the first stage. During this stage the agglutination reaction is absent or weakly positive. Leptospirae are more easily found in the urine during the second stage and become most numerous at about the thirteenth to the fifteenth day. The agglutination reaction rises from negative to weakly positive (1:100) to highly positive (1:100,000) by the fourteenth or fifteenth day of the illness. This reaction remains highly positive for about seven weeks and then slowly falls to 1:900 to 1:300 where it may remain for several years.¹¹

In order to inoculate guinea-pigs 3 to 5 c c of blood, 5 c c of spinal fluid or the sediment from 40 to 60 c c of freshly voided urine suspended in 5 c c of normal saline solution are used. After inoculation of the animal intra-

peritoneally there is an incubation period of about six days after which there is a sharp rise in temperature and jaundice occurs. This is followed in about 24 hours by collapse and death. At autopsy jaundice of the skin and internal organs is present. There are petechial hemorrhages in the skin, muscles, peritoneum, kidneys and in the gastrointestinal mucosa. There are multiple, small, sharply defined hemorrhages in the lungs, particularly in the lateral portions of the lower lobes. These hemorrhages have a rather characteristic "butterfly" distribution. There may be large hemorrhages in the adrenals. The leptospirae may be demonstrated in dark-field preparations of scrapings from the liver or kidney or by Levaditi stains of permanent sections of these organs. They may also be seen by dark-field examination of the heart blood.

Syverton et al²¹ commented upon the fact that Weil's disease was diagnosed infrequently in this country despite the wide-spread occurrence of the organism in rats. Since the leptospirae may be of low virulence they recommended that inoculated guinea-pigs be killed, if they do not die by the twelfth day, and that further guinea-pigs be inoculated with blood and kidney of the initially inoculated animals. Three such passages should be carried out before a negative report is made.

CASE REPORTS

Case 1 L. P., a 51-year-old colored woman, was admitted on October 4, 1939 complaining of chills, fever and sore throat. She was a known hypertensive who had had shortness of breath for several years. Eleven days prior to admission she became suddenly ill with chills, sore throat and fever. She had a slight dry cough and generalized and abdominal aching pains. She continued to have chills and fever until admission. Four days before admission she became disoriented and jaundice was noticed.

On admission her temperature was 101° F, pulse and respiratory rates were 90 and 28 per minute respectively. The blood pressure was 130 mm of Hg systolic and 90 diastolic. She was an obese colored female in a deep stupor. Breathing was irregular and there were periods of apnea. She was markedly jaundiced. Uremic frost was present over the face, ears and neck. There were no eruptions and there was no conjunctivitis. There was generalized hyperesthesia. The remainder of the physical examination was negative.

The urine contained one plus albumin, two plus bile, numerous clumped white cells, and occasional casts. The examination of the blood revealed 5.9 million red and 27,600 white cells per cubic millimeter with a hemoglobin content of 11 grams. There was a slight shift to the left in the differential count. The icterus index was 100 and the Van den Bergh gave a prompt direct reaction with 2.5 mg bilirubin per 100 c.c. The blood cholesterol was 210 mg per 100 c.c. The nonprotein nitrogen was 162 mg and later rose to 261 mg per 100 c.c. of blood. The stool contained bile pigments and a small quantity of blood as measured by the benzidine reaction. Blood culture was negative. *Escherichia coli* was cultured from the urine.

The patient gradually sank more deeply into coma. Her temperature ranged between 101° and 104° F. In spite of supportive therapy in the form of hypertonic glucose and intravenous saline solution she died on the fourth hospital day.

Permission for autopsy was granted and, while the necropsy was being performed, nine hours after death, Weil's disease was suggested as a cause of this patient's hitherto obscure illness. Accordingly, blood was obtained post-mortem and sent to

the National Institute of Health where an agglutination reaction against *L. ictero-haemorrhagica* was carried out with "positive results"

At autopsy the organs showed marked jaundice. There was central atrophy of the liver. Due to the obesity and jaundice there was too much postmortem change to be sure of focal necroses within the liver. An acute glomerular nephritis was present with proliferation of the glomerular epithelium, colloid degeneration of the tubular epithelium and tubular hemorrhages. Capillary hemorrhages in the brain and stomach were also present. The spleen presented the usual picture seen in patients with the sickle cell trait.

Case 2 P. E., a 48-year-old colored female, was admitted August 28, 1940 complaining of "something moving" in her stomach. Two months prior to admission she began to have severe, intermittent, aching pains in the right upper quadrant of her abdomen. These pains recurred two or three times each week. Two weeks before entry her stools became light yellow in color and her urine became dark. Nine days prior to admission she experienced two shaking chills followed by fever. At the same time the abdominal pains became more severe and frequent. Shortly thereafter she began to bleed from the mouth and the vagina and she noted urinary frequency and itching of the skin. The day before admission she was told that her eyeballs were yellow.

On admission her temperature was 100° F, pulse and respiratory rates were 96 and 24 per minute respectively. The blood pressure was 135 mm of Hg systolic and 80 diastolic. She was well developed and fairly well nourished. She was quite drowsy, responded poorly to questions, but cooperated fairly well. The sclerae were deeply jaundiced. There were numerous large and small fresh retinal hemorrhages and a large sausage-shaped rupture of the choroid in the right eye. The left eye was negative except for moderate arteriosclerotic changes in the vessels. The lungs were clear. The heart was slightly enlarged and there was a systolic murmur at the apex. The second aortic sound was somewhat ringing. There was moderate rigidity of the right upper quadrant of the abdomen but no definite tenderness. No organs or masses were felt in the abdomen. The remainder of the examination was negative.

At the time of admission the urine contained one plus albumin, 4 to 5 leukocytes per high power field and an occasional red cell. Bile was present in the urine in large quantities on admission and became negative in two weeks. Urobilin was not increased on admission but appeared in large quantities one week later and gradually returned to normal in four weeks. Beta hemolytic streptococci and *Staphylococcus albus* were cultured from the urine. The stool contained bile pigments and occult blood on admission, the blood soon disappeared. Examination of the blood revealed 4.1 million red cells and 20,000 white cells per cubic millimeter and a hemoglobin content of 14.5 grams. The differential was normal except for a slight increase in the immature forms. In two weeks the hemoglobin dropped to 9.2 grams and the white count became normal. The nonprotein nitrogen of the blood was 150 mg per 100 cc on admission and returned to normal one week later. The icterus index was 100 on admission and fell to 10 in five weeks. The Van den Bergh was direct on admission with 21.5 mg bilirubin which became indirect with a 0.6 mg bilirubin per 100 cc five weeks later. The cholesterol was 230 mg and the total protein 6.3 grams per 100 cc with an albumin-globulin ratio of 2.0/4.3. The Eagle and Wassermann reactions of the blood were positive, but the spinal fluid was negative. A roentgen-ray of the chest revealed a moderately enlarged heart and a slightly dilated aorta. There was also a stringy infiltration at the right base. Gall-bladder series revealed negative shadows in the gall-bladder which were interpreted as cholesterol stones.

Two days after admission two guinea-pigs were inoculated intraperitoneally, one with blood, and the other with urine from the patient. The guinea-pig which was inoculated with blood remained well. The guinea-pig inoculated with urine died on the

tenth day Jaundice and small hemorrhages were found throughout the organs and a few leptospirae were found by dark-field examination A third animal was inoculated with urine from the second guinea-pig This animal died on the fifth day with marked jaundice, many hemorrhages and numerous organisms

Blood sent to the National Institute of Health during the first week was found to agglutinate *L. icterohaemorrhagica* to a titer of 1 10,000 Two weeks later a second specimen was found to agglutinate the organism to a titer of 1 100,000 At the time of discharge, Dr T G Ward at the Johns Hopkins School of Hygiene and Public Health found agglutination to occur to a titer of 1 60,000, and after the syphilitic reagin was adsorbed, agglutination occurred to the same dilution

During the first week in the hospital, the patient was quite drowsy and had a low grade fever Treatment was directed toward improving kidney function and the patient responded quite well Jaundice disappeared slowly as did her abdominal symptoms Her course was complicated by a urinary tract infection and by mild cardiac failure, both responded satisfactorily to treatment She was discharged October 30, 1940 much improved

Case 3 S E, a 54-year-old white man, entered the hospital December 20, 1940 complaining of malaise Previously he had been well except for typhoid fever which he had had in 1904 He was a poultry dresser and had been occupied as such since the age of fifteen There were numerous rats about the place in which he was working He was taken ill rather suddenly 10 days before admission with cough and a small amount of sputum For a few days after the onset he had rather sharp pains in his calves and thighs as well as a headache Four or five days prior to admission, jaundice was noticed for the first time During the past week he had had frequent bouts of nausea and vomiting and several epistaxes

On admission his temperature was 102° F, pulse and respiratory rates were 116 and 24 per minute respectively Blood pressure was 105 mm of Hg systolic and 65 diastolic He was a thin white male, strikingly jaundiced, who did not appear acutely ill but was somewhat apathetic Over the trunk, arms and legs, there were numerous slightly raised, erythematous areas about two or three mm in diameter which faded on pressure There was no conjunctivitis, glandular enlargement or tenderness in the calves or thighs There was some dried blood in the nostrils and on the tongue and lips The lungs were negative except for a few medium dry râles at both bases The heart was not enlarged but there was a very short pre-systolic rumble at the apex The abdomen was easily palpated and both kidneys were felt The liver was questionably palpable two fingers'-breadth below the costal margin The remainder of the physical examination was negative

The urine was negative for albumin, cells and casts Bile and urobilin, which were present in large quantities at the time of admission, gradually disappeared during his hospital stay The stool contained bile pigments but no blood Examination of the blood revealed 3 41 million red cells, 16,400 white cells per cubic millimeter and a hemoglobin content of 12 grams The nonprotein nitrogen was 32 mg, cholesterol 220 mg and the total proteins, 5 grams per 100 cc of blood The albumin-globulin ratio was 3 1/19 Prothrombin time three days after admission was 78 per cent of normal The icterus index, which on admission was well over 100, slowly became normal before discharge The Van den Bergh gave a prompt direct reaction on admission with a bilirubin content of 23 5 mg per 100 cc This soon became indirect and subsequently returned to normal values The Eagle reaction was negative

Guinea-pigs inoculated with blood were negative Of two inoculated with urine, one died 13 days later with mild jaundice and a moderate number of hemorrhages in the lungs and intestines Dr T G Ward was able to isolate leptospirae from the heart blood of the other guinea-pig which had been inoculated with urine Serum sent to the National Institute of Health on December 30, 1940 agglutinated *L. icterohaemorrhagica*

rhagica in a dilution of 1:100,000 and *L. canicola* 1:1,000. This was repeated, using *L. ictero-haemorrhagica* only, with the same results.

During the first week the patient's temperature ranged between 100° and 102° F. The rash spread for the first two days and then gradually disappeared. Four days after admission, a parotitis developed on the right side which subsided in about six days. A moderate anemia developed and the red count fell as low as 2.4 million cells per cubic millimeter. Otherwise, his course was uneventful except for a low-grade fever which he had for most of the remainder of his stay in the hospital.

Case 4 E. P., a 58-year-old colored man, entered the hospital March 1, 1941 complaining of a "cold" and pain in his chest. He had had "chills and fever" as a young man while in Georgia. In 1922 he had a post-pneumonic empyema for which a thoracotomy was performed. About one week before admission he began to have a cough and soon thereafter he had a few shaking chills. He became increasingly weak and began to suffer from vague pains in his legs, abdomen and chest. He stated that his legs were somewhat tender at that time. There were numerous rats about the place in which he lived and he frequently found them eating the food he had intended to eat.

On admission his temperature was 101.8° F, pulse and respiratory rates were 90 and 22 per minute respectively. The blood pressure was 102 mm. of Hg systolic and 90 diastolic. He was a fairly well nourished colored male who was quite drowsy and responded poorly and vaguely to questions. The skin was dry and the conjunctivae were icteric but not injected. There was no tenderness of the muscles of the calves or thighs. There was a slight lag of the right hemithorax with an old thoracotomy scar on that side. The right base did not descend well and there were a few fine rales at the angle of the right scapula. The heart was not enlarged and there were no murmurs over the precordium. The liver was not felt but the spleen was firm and descended about three centimeters below the costal margin. The remainder of the physical examination was negative.

The urine contained a small amount of albumin, moderate amounts of bile and urobilin and occasional red and white blood cells. The urine became clear about three weeks after admission. The stool contained bile pigments but no blood. Examination of the blood revealed 5.33 million red cells, 9,160 white cells per cubic millimeter and a hemoglobin content of 13 grams. The nonprotein nitrogen was 50 mg., the total proteins were 6.0 grams per 100 cc. of blood. The nonprotein nitrogen fell to 30 mg. per 100 cc. in a few days. The icterus index, which on admission was 100, gradually became normal. The Van den Bergh gave a biphasic reaction with a bilirubin content of 3 mg. per 100 cc. of blood at the time of admission. The Eagle reaction was negative. The cerebrospinal fluid was negative. Serum sent to the National Institute of Health on March 11 agglutinated *L. ictero-haemorrhagica* to a dilution of 1:10,000, on March 18, the reaction was positive to a titer of 1:100,000. Guinea-pigs inoculated with urine did not die and we were unable to obtain the organism even after further transference to other guinea-pigs.

The patient's temperature ranged from 101° to 102° F. for two days. After that it remained at about 100° F. for two weeks before returning to normal. He soon began to gain slowly in strength. A slight anemia of 3.87 million red cells per cubic millimeter developed during the second week of his hospitalization.

Case 5 W. T., a 28-year-old colored man, entered the hospital April 28, 1941 complaining of jaundice. Ten days before admission he suddenly became ill with headache, fever and aching pains in his back and arms. These symptoms continued for five days, then gradually subsided. Following this he became very weak. He noticed that his urine was dark, and, three days prior to admission, jaundice was first called to his attention.

He worked in a restaurant but knew of no rats there. Near his home a slum clearance program was in progress and, while the buildings were being torn down, he noticed many more rats than usual in his back yard.

On admission his temperature was 99.6° F, pulse and respiratory rates were 60 and 22 per minute respectively. The blood pressure was 110 mm of Hg systolic and 70 diastolic. He was a well developed colored man who appeared to have lost a little weight. Although cooperative, he was somewhat listless and drowsy. There was marked jaundice of the sclerae. The liver lay two fingers' breadth below the costal margin and the lower poles of both kidneys were readily palpable. The physical examination was otherwise negative.

The urine contained moderate amounts of bile and urobilin but no albumin, cells or casts. The bile and urobilin disappeared by the time of discharge. The stool contained bile pigments but no blood. Examination of the blood revealed 4.01 million red cells, 13,100 white cells per cubic millimeter and a hemoglobin content of 11.8 grams. No anemia developed during his stay in the hospital. The nonprotein nitrogen was 23 mg per 100 cc of blood. The icterus index was 50 at the time of admission and reached 15 before discharge. The Van den Bergh gave a biphasic reaction with a bilirubin content of 7.1 mg on admission. The Eagle reaction was negative. Serum sent to the National Institute of Health on April 28 agglutinated *L. icterohaemorrhagica* to a dilution of 1:1,000 while that sent May 12 agglutinated the organisms to a titer of 1:10,000. Urine sediment was injected into guinea-pigs on May 1. One week later the animals died with jaundice and pulmonary hemorrhages. Numerous leptospirae were seen by dark-field examination of the emulsified kidney.

His stay in the hospital was an uneventful one, during which he rapidly regained strength and was discharged May 12, 1941.

Case 6 G. Y., a 42-year-old white man, was admitted to the hospital May 13, 1941 complaining of nausea and vomiting. He had been observed in a neurologic clinic for 16 years because of idiopathic epilepsy. He had had a slight "cold" with cough and nasal discharge for nine days prior to admission. Four days before entry, he had a sudden severe shaking chill followed by feverishness and malaise. Next day he developed an aching pain in his lower back which became severe. His cough increased and nausea and vomiting developed to such an extent that he was unable to retain anything but small amounts of liquids. There had been a moderate epistaxis on the day prior to admission. He was a sewer worker.

On admission his temperature was 102.6° F, pulse and respiratory rates were 134 and 20 respectively. The blood pressure was 108 mm of Hg systolic and 80 diastolic. He was a thin, acutely but moderately ill white male who was somewhat drowsy and slightly confused. The conjunctivae were injected but there was no icterus. There were a few sonorous râles scattered throughout the chest. The spleen and liver were not felt. The physical examination was otherwise negative.

The urine contained a small amount of albumin and occasional red and white blood cells. Bile and urobilin appeared a few days later. Examination of the blood revealed 5.1 million red cells, 7,800 white cells per cubic millimeter and a hemoglobin content of 14.6 grams. The white cells rose to 15,700 two days later. At the time of admission the nonprotein nitrogen was 50 mg per 100 cc of blood, on May 19 it was 100 mg per 100 cc. It fell to 38 mg on May 21 and then rose gradually to 120 mg on May 29, only to fall again to normal before discharge. The icterus index rose from 30, three days after admission, to 100 three days later and became normal by the time of discharge.

Dark-field examination of the blood on May 17 revealed a moderate number of *L. icterohaemorrhagicae*. A guinea-pig inoculated with urine on May 29 died 16 days later with jaundice and hemorrhages in the lungs. Numerous organisms were seen by

dark-field in the emulsified kidney Serum sent to the National Institute of Health agglutinated *L. icterohaemorrhagica* to a titer of 1 10,000 on May 25 and to a titer of 1 100,000 on May 28

The patient's temperature ranged irregularly up to 103° F during the first week in the hospital Following this, it became normal for five days and then suddenly rose to 103°-104° F where it remained for two days The temperature subsequently returned to normal for the duration of his hospital stay Jaundice first appeared three days after entry and became very deep before it finally subsided A few small erythematous maculo-papules were visible on the abdomen for two days one week after admission At the time of the "after fever" no change in the patient's condition other than increased drowsiness and a rising nonprotein nitrogen could be observed Spinal fluid examination was negative The patient was critically ill during the early part of his illness but after the second rise in temperature, his recovery was a steady one A mild anemia of 11 grams of hemoglobin has developed during convalescence

It is probable that the diagnosis of Weil's disease would be made more frequently in this country if this illness were considered more often in the differential diagnosis of jaundice of unknown etiology or of any obscure illness which may have as its features muscle pains, conjunctivitis and fever of rather sudden onset The final diagnosis rests upon the results of the laboratory procedures One should bear in mind, as a means of establishing the diagnosis, the agglutination reactions and guinea-pig inoculations with blood and urine The history of contact with the urine of wild rats, through occupation or in some other manner, is a valuable aid Sudden onset of a febrile illness with or without chill and later jaundice, with muscular pains, gastrointestinal disturbances, redness of the conjunctivae, albuminuria, and epistaxes, should suggest Weil's disease Jaundice, occurring during an acute illness, associated with hepatomegaly but without splenomegaly or general glandular enlargement should also suggest this disease Furthermore, in any case of serous meningitis, one should consider this disease very carefully

The disease may vary from an extremely mild one without jaundice and resembling influenza to a very severe prostrating illness with a fatal outcome Abrupt onset, leukocytosis and albuminuria are important points in differentiating this disease from catarrhal jaundice Nephritis occurs in 89 per cent of those cases with jaundice and in 75 per cent of those without jaundice¹⁷ The diagnosis of the disease without jaundice is extremely difficult Muscular pains, albuminuria, conjunctivitis and leukocytosis in addition to a history which may suggest a contact with the urine of rats may be helpful Probably one of the most noteworthy features of the disease is the striking apathy of the patients This was an outstanding characteristic of four of our patients One of our cases, admitted with jaundice and azotemia, was thought to be suffering from acute yellow atrophy This would suggest that any similar case without a known etiological agent should be thoroughly investigated for the possibility of Weil's disease

The prognosis is influenced by age, presence or absence of jaundice, cardiac function and the presence or absence of uremia As the age of the

patient increases, the prognosis becomes proportionately more grave. Walch-Sorgdrager¹⁷ found that the fatality rate in patients aged 10 to 40 was 10 per cent, from 40 to 60 it was 24 per cent, and in those cases over 60 it was 60 per cent. The case fatality rate for those cases without jaundice is negligible^{6,17}. The case fatality for all ages varies from 16 to 32 per cent in those cases with jaundice. In the United States, Jeghers, Houghton and Foley²⁰ found the case fatality rate to be 41 per cent. Uremia has an unfavorable influence on the prognosis particularly if oliguria or anuria is present. An increase in urinary output with a fall in the nonprotein nitrogen are favorable signs, although the patient may still die of cholemia or cardiovascular collapse.

An active immunity may be produced by the injection of killed organisms. Inada et al²¹ used immunized horse and convalescent human serum and reduced the case fatality rate from 30.6 to 17.3 per cent. More recently, however, Walch-Sorgdrager concluded, "although the evidence as a whole does not conclusively demonstrate that serum exerts any specific action upon the pathogenic organisms it seems clear that it has a beneficial effect when administered within four days of the onset of the disease." In light of the recent work on treatment of diseases of the liver with a high carbohydrate low fat diet, it is probable that such a diet would prove useful in the treatment of those cases with jaundice.

SUMMARY AND CONCLUSIONS

Six cases of Weil's disease occurring within a period of 20 months are reported. Case 1 was that of a 51-year-old colored female, extremely jaundiced, who died in uremia. The cause of the illness was obscure but at autopsy, the history of uremia and the presence of jaundice and petechial hemorrhages suggested the correct diagnosis which was confirmed by the agglutination reaction. Case 2 bore a marked similarity to the first case, and because of this fact the necessary steps in confirming the diagnosis were undertaken. Case 3 might have been diagnosed as catarrhal jaundice had we not had experience with the two previous cases. Case 4 was somewhat atypical because of the large spleen. This, however, was probably due to a malarial infection which he almost surely had had in the past. Cases 5 and 6 were more or less typical.

Goldberg and Davens²² reported two cases in children occurring at the Harriet Lane Home. These eight cases, which occurred within a short period of time in Baltimore, should help to illustrate the widespread incidence of this disease. It is our feeling that the diagnosis of Weil's disease would be made more frequently if the agglutination reaction were performed in cases of jaundice of obscure etiology, in those cases presenting some of the usual features of the disease as described, and in atypical forms of meningitis.

We wish to thank Dr A Packchamian and Dr Carl Larson of the National Institute of Health and Dr T G Ward of the Johns Hopkins University, School of Hygiene and Public Health for their assistance in this work

REFERENCES

- 1 WEIL, A Ueber eine eigenthumliche, mit Milztumor, Icterus und Nephritis einhergehende, akute Infectiouskrankheit, Deutsch Arch f klin Med, 1886, xxxix, 209-232
- 2 (a) INADA, R, IDO, Y, HOKI, R, KANEKO, R, and ITO, H The etiology, mode of infection and specific therapy of Weil's disease, Jr Exper Med, 1916, xxiii, 377-401
- (b) ITO, T, and MATSUZAKI, H The pure cultivation of *Spirochaeta ictero-haemorrhagiae*, Jr Exper Med, 1916, xxiii, 557-562
- (c) IDO, Y, HOKI, R, ITO, H, and WANI, H The prophylaxis of Weil's disease, Jr Exper Med, 1916, xxiv, 471-483
- (d) INADA, R, IDO, Y, HOKI, R, ITO, H, and WANI, H The serum treatment of Weil's disease, Jr Exper Med, 1916, xxiv, 485-496
- (e) KANEKO, R, and OKUDA, K The distribution in the human body of *Spirochaeta ictero-haemorrhagiae*, Jr Exper Med, 1917, xxvi, 325-339
- (f) IDO, Y, HOKI, R, ITO, H, and WANI, H The rat as a carrier of *Spirochaeta ictero-haemorrhagiae*, the causative agent of Weil's disease, Jr Exper Med, 1917, xxvi, 341-353
- (g) INADA, R. The clinical aspects of *Spirochaetosis ictero-haemorrhagica* or Weil's disease, Jr Exper Med, 1917, xxvi, 355-361
- (h) INADA, R, IDO, Y, HOKI, R, ITO, H, and WANI, H Intravenous serotherapy of Weil's disease, Jr Exper Med, 1918, xxvii, 283-303
- (i) KANEKO, R, and OKUDA, K Distribution of *Spirochaeta ictero-haemorrhagiae* in the organs after intravenous serum treatment, Jr Exper Med, 1918, xxvii, 305-308
- 3 NOGUCHI, H *Spirochaeta ictero-haemorrhagica* in American wild rats and its relation to the Japanese and European strains, Jr Exper Med, 1917, xxv, 755-763
- 4 NOGUCHI, H Morphological characteristics and nomenclature of *Leptospira (Spirochaeta) ictero-haemorrhagiae*, Jr Exper Med, 1918, xxvii, 575-592
- 5 WADSWORTH, A, LANGWORTHY, V, STEWART, C, MOORE, A, and COLEMAN, M Infectious jaundice occurring in New York State, Jr Am Med Assoc, 1922, lxxviii, 1120-1121
- 6 SCHUFFNER, W Recent work on leptospirosis, Trans Roy Soc Trop Med and Hyg, 1934, xxviii, 7-37
- 7 JOBLING, J W, and EGGSTEIN, A A The wild rats of the southern states as carriers of *Spirochaeta ictero-haemorrhagiae*, Jr Am Med Assoc, 1917, lxix, 1787
- 8 OTTERAEN, A The spirochaete of infectious jaundice in house rats in Chicago, Jr Infect Dis, 1919, xxiv, 485-488
- 9 MEYER, K. F, EDDIE, B, and STEWART-ANDERSON, B Canine, murine and human leptospirosis in California, Proc Soc Exper Biol and Med, 1938, xxxviii, 17-19
- 10 ROBINSON, G H Occurrence of *Leptospira ictero-haemorrhagiae* in wild rats of Baltimore, Am Jr Hyg, 1924, iv, 327-329
- 11 FAIRLEY, N H Weil's disease among sewer workers in London, Brit Med Jr, 1934, ii, 10-14
- 12 GLOTZER, S. Weil's disease, report of a case in a fish worker, Jr Am Med Assoc, 1938, cx, 2143-2145
- 13 EITON, N W. Spirochaetal jaundice in Buffalo, N Y report of a fatal case in a fish merchant, Am Jr Clin Path, 1939, ix, 219-225
- 14 DAVIDSON, L, and SMITH, J Weil's disease in fish-workers, a clinical, chemical, and bacteriological study of 40 cases, Quart. Jr Med, 1936, v, 263-286
- 15 PACKCHAMIAN, A The prevalence of infectious jaundice in the United States as determined by agglutination and animal inoculation tests, Am Jr Path, 1938, xiv, 638-642

- 16 JORGE, R Une epidemie à Lisbonne, Bull Mensuel Office Internat d'Hyg Publique, 1932, xxiv, 88-117 Quoted by Schuffner
- 17 WALCH-SORGDRAGER, B Leptospiroses, Bull of Health Organization, League of Nations, 1939, viii, 143-386
- 18 MURGATROYD, F Chronic meningitis in Weil's disease, Brit Med Jr, 1937, i, 7-11
- 19 MORTENSEN, V Nervous complications of Weil's disease, Lancet, 1940, i, 117-119
- 20 JEGHERS, H J, HOUGHTON, J D, and FOLEY, J A Weil's disease report of a case with postmortem observations and review of recent literature, Arch Path, 1935, xx, 447-476
- 21 SILVERTON, J T, BERRY, G P, and STILES, W W The diagnosis of Weil's disease (infectious jaundice) Concerning the use of guinea-pigs for the detection of strains of *Leptospira icterohaemorrhagiae* of low virulence, Jr Clin Invest, 1938, xvii, 522-523
- 22 GOLDBERG, H P, and DAVENS, E D Case presentation, Weil's disease, Proc of Meeting of Johns Hopkins Med Soc, Nov 1940, Bull Johns Hopkins Hosp, 1941, lxxvii, 112

THE DIAGNOSIS AND MANAGEMENT OF BRUCELLOSIS *

By WALTER M SIMPSON, M S , M D , F A C P , *Dayton, Ohio*

THE past decade has witnessed a remarkable advance in our knowledge of the incidence of brucellosis. The author's prediction,¹ in 1930, that brucellosis would probably soon become recognized as a public health problem of major proportions, was based upon the discovery of 90 cases of the disease in and about Dayton during a period of 18 months. Prior to this investigation the disease was not known to be prevalent in this area. The results of other surveys conducted during recent years in widely separated parts of the United States provide unmistakable evidence of the widespread distribution of brucellosis and leave little doubt that this disease is a common and a frequently unrecognized source of disabling illness.

That milk-borne brucellosis may be practically eliminated from a community by the adoption of a universal pasteurization ordinance is demonstrated by the Dayton experience. During the four years prior to the passage of such an ordinance in Dayton, in 1931, 196 cases of brucellosis were encountered. All but one of the 52 cases studied by the author during the past decade have occurred in persons who consumed raw milk or other unpasteurized dairy products elsewhere, usually while vacationing, prior to the onset of illness. The single exception was an employe of a local dairy who drank milk before it was pasteurized.

Prior to 1926, the sporadic cases which were encountered were regarded as clinical curiosities. Most of these were related to endemic foci of goat infection in Texas, New Mexico, and Arizona. From 1927 to 1930, the number of recorded cases rose from 217 to 1385. During 1929, cases of brucellosis were encountered in every state of the Union. In 1940, 3358 cases were officially reported to the U S Public Health Service by State Health Departments.² It is undoubtedly true that the number of cases actually occurring is much larger than that reported.

Among urban populations, the chief mode of transmission of the disease is by the ingestion of raw milk and unpasteurized dairy products derived from cattle infected with *Brucella abortus*. Of the 248 patients with brucellosis studied personally by the writer, the ingestion of raw milk or unpasteurized dairy products containing the organism of contagious abortion of cattle was demonstrated to be the source of infection in the great majority of instances. Direct dermal transmission may be the mode of infection among dairymen, veterinarians or slaughter house workers. Hardy expresses the

* Presented before the Twenty-Fifth Annual Session of the American College of Physicians, as a part of the Symposium on Infectious Diseases, Boston, April 25, 1941.

belief that direct contact with infected cattle and hogs has been responsible for a great number of cases of brucellosis occurring in Iowa Hardy³ has demonstrated by animal experiments that the skin may act as the portal of entry of the organism Morales-Otero,⁴ of Puerto Rico, has reproduced the disease in human volunteers by inoculations through abraded skin It is apparent, therefore, that there are two important sources of infection for man commonly by the ingestion of raw milk or unpasteurized dairy products containing *Brucella*, or less frequently as the result of direct contact with infected fresh animal tissues or discharges There is no definite evidence of man-to-man transmission of the disease

CLINICAL MANIFESTATIONS IN MAN

Because brucellosis presents many symptoms and signs common to typhoid fever, malaria, tuberculosis and influenza, it is frequently confused with these diseases Many physicians have arrived at a tardy diagnosis of brucellosis only after repeated negative Widal reactions, the failure to demonstrate the malarial plasmodium, and the inability to elicit physical signs or roentgen-ray evidence of tuberculosis Less often, the disease has been confused with acute rheumatic fever, subacute bacterial endocarditis, bronchitis, pyelitis, appendicitis, cholecystitis, or tularemia

SYMPTOMATOLOGY

As knowledge of the clinical manifestations of brucellosis has advanced, particularly during the past decade, it has become more and more apparent that the older textbook descriptions of the symptomatology of the disease were based largely upon experiences with brucellosis of goat origin The classical clinical picture of a disease characterized by an undulatory, remittent, or intermittent fever, drenching sweats, chills, headache, backache, muscular and joint pains, weakness, loss of weight, possibly a palpable spleen, an infrequent skin eruption, leukopenia with lymphocytosis, and anemia, pertains chiefly to the severe acute forms of the disease In a high proportion of cases, the disease pursues a relatively mild, prolonged course, extending over many months or years The early descriptions by Hughes⁵ and Craig⁶ included many such cases Alice Evans and others have more recently directed particular attention to the common chronic ambulatory form of brucellosis, in which the patient, whose spirits are already depressed by continued ill health, is often given further discouragement when a diagnosis of neurasthenia is made Many "neurasthenics," whose chief complaints were exhaustion, insomnia, irritability, and a variety of aches and pains have been found to be victims of chronic brucellosis

Since the symptomatology of the acute and the chronic forms of brucellosis varies so greatly, these two manifestations will be considered separately

ACUTE BRUCELLOSIS

The incubation period has been found to vary from five days to longer than one month. In accidental laboratory infections the incubation period has varied from 10 to 20 days. The prodrome is not unlike that of any general infection, with a gradual onset, although in occasional cases the disease is initiated with a sharp chill and rapid elevation of temperature to 103–105° F (39.4–40.6° C). A sense of tiredness and weakness, loss of appetite, constipation, headache and backache are common early symptoms. Usually, the patient becomes gradually aware of an afternoon or evening rise in temperature, associated with chills or chilly sensations, nocturnal perspiration and weakness. The patient often feels quite well during the morning hours, particularly in the early stages of the infection. As the temperature rises, during the afternoon or evening, the symptoms gradually return and increase in severity. The nocturnal exacerbations of fever occasionally reach great heights (106–107° F, 41.1–41.7° C). There is often a remarkable disparity between the subjective sense of fever and the height of the fever as registered by the clinical thermometer, in many instances the patient does not complain of fever, nor does he present a febrile appearance, but the physician finds, to his surprise, a fever of 101–103° F (38.3–39.4° C). As the fever abates, chills and sweating occur. If defervescence is rapid, the perspiration is more likely to be of a drenching character. In such cases, the sweats, which literally saturate the night clothing and bedding, are one of the most impressive features of the disease. The perspiration often has a peculiar sweetish, fetid odor. The chills may be severe enough to be regarded as true rigors in about one-third of the acute cases^{1, 7, 8}. Many patients experience only mild chilly sensations, while in about one-fourth of cases chilliness is absent.

Arthralgia and muscular pains are prominent features of the acute form of the disease in approximately one-half of the cases. The joint pains may be more pronounced during the onset or they may persist throughout the course of illness. The myalgia may be accompanied by a feeling of "stiffness" not unlike the muscular soreness which follows vigorous exercise. Hydrarthrosis and transient periarticular swelling have been observed occasionally. Green and Freyberg⁹ investigated the incidence of brucellosis in patients with rheumatic disease; they found that while *temporary* non-purulent joint inflammation does occur, chronic arthritis rarely, if ever, occurs as a complication of brucellosis. We have encountered no instances of permanent joint impairment. Suppurative osteomyelitis as a complication of brucellosis has been described with increasing frequency during the past few years^{10–16}. In most of the reported cases the vertebrae, particularly in the lumbar region, were attacked. In some instances other bones, such as the humerus, femur, skull and ribs, were affected. Feldman and Olson^{19, 20} found similar examples of *Brucella* spondylitis in 24 hogs, an average occurrence of one in every 6000 swine slaughtered.

Marked restlessness and insomnia usually accompany the nocturnal febrile exacerbations. Delirium occurs in some cases in which the fever reaches great heights. Regional *Brucella* localizations in the brain, spinal cord or meninges may occur during the acute phase of the disease and produce symptoms and signs of encephalitis, myelitis or meningitis, such complications are, however, more commonly observed as delayed manifestations of brucellosis. The meningeal involvement predominates, and the development of encephalitis or myelitis, or both, is usually secondary to the meningitis. The involvement of the central nervous system may produce the first and only symptoms of the disease. The symptomatology varies greatly, depending upon the extent of meningeal invasion and the presence of additional complications involving the brain, spinal cord or peripheral nerves. In a patient with brucellosis, the development of such symptoms and signs as severe headache, vertigo, diplopia, nuchal rigidity, aphasia, psychic disturbances and various forms of paralysis which are often evanescent, calls for examination of the cerebrospinal fluid. Characteristically, the spinal fluid will be under increased pressure and will show pleocytosis, increase of albumin and a decrease of globulin and sugar. Since the ultimate diagnosis during life depends upon the isolation and identification of *Brucella* from the spinal fluid, a particularly diligent effort should be made to recover the organism by culture and by guinea pig inoculation. DeJong²¹ has recorded 11 verified cases of *Brucella* meningitis or meningoencephalitis in which the organism was recovered from the spinal fluid by culture or by guinea pig inoculation.

A growing body of evidence indicates that ocular complications of brucellosis are not uncommon. We have encountered at least eight instances of ocular disease occurring as a manifestation of brucellosis. Green²² has found that the cornea, the uveal tract, the retina, the optic nerve and the external ocular muscles are vulnerable to attack. In addition to four cases (corneal ulcer, retinitis, optic neuritis and central retinochoroiditis) encountered in his own practice, Green describes 27 additional cases reported in the literature. Rutherford²³ found papilledema in three of 63 cases of brucellosis examined ophthalmoscopically. Rutherford suggests inclusion of brucellosis in the differential diagnosis in cases of papilledema in which the symptomatology is indefinite. Ruedemann²⁴ states that brucellosis is responsible for uveitis much more commonly than is generally believed, he found brucellosis to be responsible for chronic uveitis in seven of 125 patients with uveal tract disease.

The matutinal remissions or intermissions and the nocturnal exacerbations of fever may last from one week to many months. The inadequate name "undulant fever" refers to recurring relapses of fever following afebrile intermissions. Such febrile relapses are the exception rather than the rule, most patients experience but one febrile period, lasting from a few days to several months, and finally reaching the normal level by lysis.

The essential gastrointestinal complaints are anorexia and constipation.

The degree of constipation appears often to parallel the severity of the infection. Diarrhea is of rare occurrence. Nausea and vomiting may occur in the more severe cases. Abdominal pain is a not infrequent feature of the disease during its early manifestations. Among 125 cases studied by Hardy, abdominal pain occurred in 40, in 10 it was the major complaint. Simpson found abdominal pain to be the chief complaint in 16 of 142 patients with brucellosis. The occurrence of abdominal pain has often led to appendectomy in patients with unsuspected brucellosis, the correct diagnosis having been made only after the persistence of febrile symptoms stimulated a further search for the cause. As in typhoid fever, the gall-bladder may become a focus of *Brucella* infection. *Brucella* has been recovered from the excised gall-bladder and from the bile following duodenal drainage in patients with symptoms of cholecystitis^{25, 26, 27}

Symptoms referable to the respiratory tract may be an outstanding feature of the disease in certain instances. Cough, associated with mucoid or muco-purulent sputum production, is not infrequent during the first few weeks of illness, and may persist for months. Recent reports²⁸⁻³² provide convincing evidence that pulmonary lesions of brucellosis are of frequent occurrence and are often detectable by roentgenographic examination, even in the absence of distinctive physical signs of pneumonia. The lesions most often encountered on roentgen-ray examination are peribronchial infiltrations, hilar infiltrations, and scattered discrete or confluent patchy pneumonic areas. The pulmonary manifestations of brucellosis should be regarded as hematogenous lobular pneumonia rather than true bronchopneumonia. Without doubt, pulmonary lesions occur much more commonly than is generally realized. Serial roentgenographic studies will often provide an explanation for vague respiratory symptoms.

The most serious cardiovascular complication has been the occasional occurrence of vegetative endocarditis. Smith and Curtis³³ found reports of nine cases of *Brucella* endocarditis confirmed by postmortem examination, to which they added a similar case. In most instances the vegetations occurred on mitral or aortic valves previously damaged by rheumatic fever.

The name commonly applied to brucellosis of cattle, "infectious abortion," is derived from the well known predilection of the causative organism for the genital tract. There is strong evidence that the same regional localization sometimes occurs in human beings. Painful swelling of the testes has been described frequently. Acute epididymitis, orchitis, prostatitis and seminal vesiculitis may be early manifestations of the disease. Simpson¹ recovered *Brucella abortus* from a draining sinus tract which extended from the globus major of the epididymis through the scrotal wall.

There appears to be little doubt that brucellosis is at least an occasional cause of abortion in women who live on farms where they have direct contact with infected animals, or in women who consume raw milk or unpasteurized dairy products. There are reports^{34, 35} of human abortion in which

the history and serologic findings provide strong circumstantial evidence of the etiologic rôle of *Brucella*. In a study of 565 cases of brucellosis, Calder³⁸ found a history of one or more miscarriages in 32 per cent of the married women, a history of one miscarriage followed by sterility was common, a few women reported as many as five or six abortions. More direct evidence has been provided by Carpenter and Boak³⁹ who recovered *Brucella abortus* from the tissues of a human fetus which was aborted at the end of the fourth month of gestation. Kristensen⁴⁰ isolated the *abortus* variety of the organism from the exudate which covered the uterine site of the placenta of a seven-month fetus. Fier⁴¹ isolated *Brucella* from the vaginal discharge of a woman who had aborted 10 days previously.

Loss of weight is an almost constant feature of the acute form of the disease. The greatest loss, often from 10 to 50 pounds, occurs in those patients who experience high fever, drenching sweats and great prostration.

A transient cutaneous eruption, usually papular, macular or maculopapular, is a relatively infrequent finding. The skin lesions may simulate the roseola of typhoid fever.

CHRONIC BRUCELLOSIS

Many physicians feel that the symptoms and signs of acute brucellosis are often sufficiently characteristic to justify such a provisional diagnosis on the basis of clinical findings. In dealing with chronic brucellosis, however, the physician is often faced with a problem which will tax his diagnostic acumen to the utmost. No disease, not excepting syphilis and tuberculosis, is more protean in its manifestations.

Quite naturally, a certain amount of wholesome skepticism has arisen in the minds of some physicians regarding any wide prevalence of chronic brucellosis. Such a feeling of doubt is quite defensible, since one is justified in questioning the validity of some of the diagnostic tests upon which such a diagnosis is often based.

The common and unfortunate employment of the name "undulant fever" has served only to add further difficulties in the recognition of cases of chronic brucellosis. A significant temperature curve, physical signs of disease, and positive agglutination tests and skin tests may be entirely lacking throughout a long period of chronic illness. The recent studies by Evans,^{42, 43, 44} Poston,⁴⁵ Angle,⁴⁶ Scoville,⁴⁷ Thames,⁴⁸ Calder,³⁸ Hamman and Wainwright,⁴⁹ Harris,⁵⁰ Cameron and Wells,⁵¹ Gould and Huddleson,⁵² Gersh and Mugrage,⁵³ and Angle, Algie, Baumgartner and Lunsford⁵⁴ leave little doubt that a protracted, relatively mild, partially disabling, often ambulatory, form of brucellosis is widely prevalent and constitutes a major cause of chronic ill health. Only a small proportion of patients with chronic brucellosis, probably less than 10 per cent, have experienced a previous acute febrile illness, compatible with a diagnosis of acute brucellosis. In many cases the patient is not entirely incapacitated for work, but complains chiefly

of weakness and exhaustion, with or without mild fever. Since the commonly employed diagnostic tests are frequently negative in such cases, and since even the most conscientious physician may not find physical abnormalities to account for the patient's complaints, the almost inevitable diagnosis of neurasthenia or psychoneurosis is too often made.

A recitation of all of the symptoms which have been ascribed to chronic brucellosis would serve only to heighten the confusion which as yet surrounds this baffling phase of the disease. In general, it may be stated that the three cardinal features of most cases of chronic brucellosis are weakness, low-grade fever and a lack of objective physical findings. McGinty and Gambrell⁵⁵ have listed over 150 different manifestations of chronic brucellosis. Mild degrees of fever may be present for many weeks or months; there may be several months of complete freedom from fever, sudden febrile exacerbations may occur, accompanied by an accentuation of the prevailing symptoms, or by the development of evidence of new regional symptoms affecting the respiratory, cardiovascular, genitourinary, gastrointestinal, skeletal or nervous systems. Pneumonia, endocarditis, orchitis, epididymitis, prostatitis, oophoritis, cholecystitis, hydrarthrosis, arthritis, spondylitis, osteomyelitis, ocular complications or meningoencephalitis may be associated with the acute form of the disease, but much more commonly appear several months, or even years, after the often indefinite onset of the chronic form of brucellosis. In some instances such delayed evidences of regional *Brucella* localization may appear long after apparent recovery from the acute manifestations of the disease. All students of chronic brucellosis have emphasized the almost universal prominence of symptoms which relate to the central nervous system. In addition to the occasional acute invasion of the meninges, brain and spinal cord by *Brucella*, there is evidence⁵⁶ that the endo-antigen of *Brucella* organisms circulating in the blood has a toxic action upon the central nervous system. These observations led Evans⁴² to state "These facts challenge the right of a physician to make a diagnosis of neurasthenia—a diagnosis regarded as dishonorable by the patient, and also by his family, his employer and his friends—without considering, among other possibilities, the possibility of chronic brucellosis."

Chronic brucellosis should be suspected in all cases of so-called "fever of unknown origin." There are many reports of the isolation of *Brucella* from the blood, urine, bile or from extirpated tissues in patients who have experienced unexplained, long-continued, low-grade fever for years. Hamman and Wainwright⁴⁹ reexamined 36 such patients, an accurate diagnosis was finally made on 10 of them, three were found to have brucellosis.

DIAGNOSIS

Since it is hazardous to base a diagnosis of brucellosis solely on clinical grounds, recourse must be had to laboratory diagnostic tests. These procedures include (a) primary isolation of the causal organism by cultural

methods from blood, spinal fluid, secretions, excretions, or excised tissues, (b) indirect recovery of *Brucella* by culture after animal inoculation, (c) the agglutination test, (d) the intradermal test, and (e) the opsonocytophagic reaction

The only method by which the diagnosis of brucellosis may be completely established is by the *cultivation and identification of the organism*. While cultural technics have improved greatly during the past few years, with a corresponding increase in the number of reported instances of recovery of the organism, the undertaking is often beset with difficulties and requires skill and, above all, patience. The *melitensis* and *suis* varieties of *Brucella* ordinarily grow readily under aerobic conditions, while the much more commonly encountered *abortus* variety requires an atmosphere containing 10 per cent carbon dioxide. The procedure used by Poston⁴⁵ with notable success is as follows: 15 c c of blood are obtained from each patient by venipuncture and placed in a small flask containing 4 c c of sterile 2.5 per cent sodium citrate solution. Four flasks containing 100 c c of liver infusion broth of pH 6.8 are each inoculated with 2 c c of the citrated blood. The flasks are incubated at 37° C, two in the room atmosphere and two in an atmosphere containing 10 per cent CO₂. After four days' incubation, daily smears of the broth cultures are made and stained by Gram's method. If no organisms are seen in the smears after 10 days' incubation, 5 c c of the original culture are transplanted to 100 c c of liver infusion broth every three days for two weeks. Original cultures and transplants are incubated for three weeks before they are reported as negative.

The guinea pig is the most suitable laboratory animal for inoculation. Poston inoculates three guinea pigs with blood from each patient, two are injected intraperitoneally with 2 c c each of citrated blood, one is inoculated in the groin with 1 c c of citrated blood. The animals are observed daily. Beginning two months after inoculation, tests for specific agglutinins and for cutaneous reaction to Huddleson's brucellergin are made at intervals of a few days. When both tests become positive the animals are killed. Animals which remain negative to the agglutination test and to the skin test are killed four and one-half months after inoculation. Liver infusion broth is planted with the guinea pig's blood and with pieces of organs and is subjected to the cultural procedures previously described. The cultures may then be differentiated into *abortus*, *suis* or *melitensis* varieties by the agglutinin-absorption technic, the bacteriostatic action of dyes, glucose utilization and hydrogen sulphide metabolism^{57, 58, 59}

The most commonly used and the most reliable indicator of *Brucella* infection, in the absence of positive cultures, is the *agglutination test*. This is particularly true in cases of acute brucellosis, in which a high serum agglutinin titer will be found in a great majority of cases. Considerable diagnostic significance may be attributed to a progressive increase in the agglutinin titer upon repeated testing in suspected cases of acute brucellosis. Agglutinins

may appear as early as the fifth day of illness, but ordinarily are not found until the second week after the onset. In some instances, specific agglutinins may not appear for several weeks. One important source of difficulty in interpreting the results of agglutination tests is the fact that agglutinins may be persistently absent or may be present in low titer in persons from whom *Brucella* has been cultivated. Another source of error in interpreting the agglutination reaction is the fact that the titer may remain at a high level for months or years after recovery. Then, too, some individuals exposed to the infection may develop agglutinins without notable illness. Furthermore, the level of the agglutinin titer may fluctuate widely on repeated testing. *These considerations call for the exercise of keen judgment in interpreting the results of the agglutination test. A person suffering from some disease other than brucellosis may have a positive agglutination test merely as the result of a previous symptomatic or asymptomatic Brucella infection.*

In the past, diagnostic significance has usually been attributed to titers of 1:80 or above. The choice of such an arbitrary diagnostic titer is not justified in the light of recent studies. In those cases in which the clinical manifestations suggest brucellosis, the absence of agglutinins or their presence in titers of 1:10 to 1:40 should stimulate further bacteriologic and serologic studies.

The difficulties which attend the interpretation of agglutination tests in cases of acute brucellosis are greatly multiplied in cases of chronic brucellosis. While the great majority of patients with the acute form of the disease reveal a positive agglutination test in high titer, a high proportion of patients with chronic brucellosis give repeatedly negative agglutination reactions or positive tests in low titer. In a group of 28 cases of chronic brucellosis studied by Evans,⁶⁰ 46 per cent gave a negative agglutination reaction.

The occasional cross agglutination of *Brucella* and *Bacterium tularensis* should be borne in mind. In cases of tularemia the relatively higher titer with the *B. tularensis* antigen and the usually typical history leave little doubt as to the interpretation of the serologic findings. If the *Brucella* and *B. tularensis* titers are the same, or nearly so, agglutinin absorption tests will distinguish between them.

While the agglutination test is undoubtedly of great value, its limitations must be recognized. Otherwise, errors will be made in two directions: first, the correct diagnosis of brucellosis may not be made because too much reliance is placed in a negative test, or second, an incorrect diagnosis of brucellosis may be made in a person who has a residual agglutinin titer from a previous infection by Brucella, but who is suffering from some other disease when the test is made.

The intradermal test is used to determine cutaneous hypersensitiveness to specific *Brucella* hazards. A positive allergic skin reaction is generally accepted as evidence of past or present invasion of tissues by *Brucella*. While the great majority of patients from whose blood *Brucella* has been recovered

show a positive skin test, the test has yielded negative results in rare instances in which *Brucella* infection was proved by culture

The chief sources of error in interpreting the significance of a positive skin test lie in the fact that the test is frequently positive in exposed individuals with no history of an illness compatible with brucellosis. Furthermore, the hypersensitiveness, once acquired after symptomatic or subclinical infection, usually persists for many years. *Therefore, it must be emphasized that a positive skin test does not mean that the symptoms from which the patient is suffering at the time of a positive skin test are necessarily due to brucellosis.* Students of this disease are only too familiar with instances in which a diagnosis of brucellosis was made only on the basis of a positive skin test and in which further developments revealed the presence of some such disease as active tuberculosis, Hodgkin's disease, leukemia, typhoid fever, malaria, or subacute streptococcic endocarditis. Gould and Huddleson⁵² regard the skin test as the most sensitive diagnostic test for brucellosis, these investigators express the belief that if the skin test is negative, brucellosis may usually be ruled out

A variety of antigens has been used for skin testing. The two agents most commonly employed are (1) a heat-killed suspension of *Brucella* in physiologic saline solution (vaccine) and (2) a suspensoid of nucleoprotein isolated from *Brucella* by chemical separation, known as Brucellergin (Huddleson). If commercially available vaccines are used for skin testing, the usual procedure is to dilute the vaccine in a proportion of one part vaccine to nine parts sterile physiologic solution of sodium chloride and to inject 0.1 c.c. of the diluted suspension intracutaneously in the ventral surface of the forearm. It is important to select properly standardized vaccines from a reliable source. Variations in the manner of preparation, potency and dosage have led to a lack of uniformity in the production and interpretation of cutaneous reactions. The Brucellergin test is also performed by injecting 0.1 c.c. into the skin of the forearm. A positive reaction by either method is characterized by the development of a circumscribed erythematous, edematous, indurated area at the site of injection. In a positive test, the area of local reaction averages about three-fourths of an inch in diameter, but may vary from one-half inch to three or more inches. The reaction usually reaches its greatest intensity in 24 to 48 hours, ordinarily it is best to observe the results of the test 48 hours after injection. The presence of mild, transient erythema, without edema and induration, is of no significance. In frankly positive cases the induration usually persists for several days. In hypersensitive persons a positive test may be accompanied by a mild, or in some instances a severe, systemic reaction. In such cases the lymphatic channels above the site of inoculation may become red, thickened and painful, and the regional axillary lymph nodes may become enlarged and tender. An exacerbation of symptoms may follow the development of a positive skin test. Focal necrosis of the Arthus type occurs at the site of inoculation in a small number of cases

There is evidence^{61, 62} that the injection of heat-killed *Brucella* for the intradermal test stimulates the production of agglutinins. Evans⁴⁴ found that the intracutaneous injection of brucellergen in 12 volunteers caused the development of opsonins in seven and agglutinins in five, in one instance the agglutinins rose from zero to a titer of 1:320. Hence, blood specimens for serologic tests should be collected before the intradermal test is performed.

The inadequacies of the agglutination test and the intradermal test, particularly in distinguishing between present and past *Brucella* infection, led Huddleson, Johnson and Hamann⁶³ to reintroduce the *opsonocytophagic reaction*, a modification of the Leishman-Veitch technique for determining the phagocytic activity of the blood in the presence of serum opsonins and homologous leukocytes. The opsonocytophagic test is employed in conjunction with the intradermal test or the agglutination test, or both, to determine the immunity status of an individual giving positive tests by either or both methods. The test is performed by mixing 0.1 c.c. of the patient's citrated blood with 0.1 c.c. of a saline suspension of living *Brucella* which have been grown for 48 hours on liver infusion agar. The suspension should contain at least six billion organisms per c.c. of physiologic saline solution (pH 7.0). The mixture is then incubated at 37° C (98.6° F) for 30 minutes, after which a small amount of the sedimented cells is removed with a capillary pipette. A smear is then made from a large drop of the cell suspension, dried rapidly and stained with Hasting's stain or Bordet-Gengou's carbol toluidin blue. The number of bacteria in 25 polymorphonuclear neutrophilic leukocytes is determined and classified according to the number of bacteria per polymorphonuclear leukocyte; the absence of phagocytosis indicates a negative result, 1 to 20 phagocytized bacteria indicate slight, 21 to 40 moderate, and 41 or more, marked phagocytosis.

According to Huddleson's interpretation, the opsonocytophagic power of the blood is low during the active infective phase of the disease and becomes marked after recovery. On this basis, it is considered that individuals have developed immunity to *Brucella* if 60 per cent or more of the polymorphonuclear leukocytes show marked phagocytosis. If as many as 40 per cent of the leukocytes show moderate to marked phagocytosis the patient may be infected and has not yet developed any immunity, or he may be uninfected.

While theoretical considerations lend support to the contentions of Huddleson and his associates as to the value of the opsonocytophagic test, it still lacks confirmation. The studies by Calder,⁶⁴ and Keller, Pharris and Gaub^{61, 65} appear to provide some support to Huddleson's thesis. On the other hand, Evans⁶⁶ regards the opsonocytophagic test as the least reliable of the diagnostic tests in cases of chronic brucellosis; she found strongly positive (immune) reactions in four cases from which *Brucella* were cultivated, and weak or moderate reactions in recovered cases. Morales-Otero and Gonzalez⁶⁶ tested over 200 individuals (cattle handlers, milkers and laboratory workers exposed to *Brucella* infection) with a purified *Brucella* skin-test antigen, agglutination tests, complement fixation tests and opsonocytophagic

tests They found no correlation between cutaneous allergy to *Brucella* and the opsonocytophagic reaction Fifteen cases that were positive to the opsonocytophagic reaction gave a negative cutaneous reaction, while 18 showing a positive cutaneous reaction were completely negative to the opsonocytophagic reaction Lee Foshay^{67, 68} and the writer, working independently, have found that a significant proportion of patients yield aberrant and unexpected results in relation to their immunity status when the opsonocytophagic test is employed in conjunction with cultural methods, agglutination tests and skin tests High phagocytic titers (immune reactions) occur in some patients with severe and uninterrupted brucellosis, proved by cultures Certain recovered patients, asymptomatic for months or years, exhibit marked fluctuations from month to month, running the entire gamut from high to low phagocytosis, or sometimes none at all *Until more extensive studies have been made on culturally proved cases of brucellosis the results of the opsonocytophagic test should be interpreted with caution and with reservations*

Hematocytologic studies indicate that leukopenia occurs in the majority of patients with acute brucellosis In chronic brucellosis, either leukopenia, moderate leukocytosis or normal leukocyte levels may be found Calder⁶⁹ has directed particular attention to the occurrence of active lymphocytogenesis as the most striking and constant feature of the blood picture in all of the manifestations of brucellosis The lymphocytosis is evidenced by an increase in both percentage values and in absolute numbers of lymphocytes and by an unusually high proportion of immature lymphocytes (lymphocytic shift-to-the-left) Mild anemia of the macrocytic, hyperchromic type is the rule The erythrocyte sedimentation rate is usually not high, except when regional complications are present Calder expresses the belief that this combination of white blood cell and red blood cell abnormalities is distinctive for brucellosis and provides an additional confirmatory diagnostic aid

PROGNOSIS

Fatal outcome is rare, having occurred in about 2 per cent of reported cases During 1936, 107 deaths from brucellosis were officially recorded in the United States The importance of the disease is not to be judged by the low mortality rate The prolonged course and the resulting chronic ill health in a high proportion of cases make the outlook much more serious than the death rate would indicate Death is usually the result of overwhelming acute infection, terminating fatally during the first few weeks of illness, or it follows a relapse at any stage of the disease due to regional localizations of *Brucella* in such structures as the meninges, brain, heart valves or lungs

TREATMENT

The most important consideration in the control of brucellosis is *prophylaxis* The widespread distribution of the infection among cattle renders it

difficult to control the infection at its source. Many cows have Bang's disease and eliminate the organisms in large numbers in the milk and vaginal discharges without manifesting symptoms of the disease (abortion, mastitis, sterility and lessened milk yield).

Since 1934, the United States Department of Agriculture has been engaged in a laudable campaign directed toward eradication of brucellosis in cattle. After 55 months of diligent effort, ending January 31, 1939, more than a million and a half cattle (approximately 55 per cent of the number tested) were found to give positive tests for brucellosis, the infected cattle were condemned and the farmers and dairymen received indemnities to compensate for the loss of the cattle. Unfortunately, no similar campaign has yet been inaugurated to control the disease in hogs and goats.

The logical method for preventing the transmission of milk-borne infection to human beings is by pasteurization. Brucellosis is only one of the formidable list of diseases transmitted to man through the use of raw milk and other unpasteurized dairy products. Murray, McNutt and Purwin,⁷⁰ Boak and Carpenter,⁷¹ and Zwick and Wedeman⁷² have demonstrated that complete pasteurization (143–145° F (61.6–62.7° C) for 30 minutes) will destroy *Brucella*. *The need for strict supervision of the pasteurization process is apparent.* For the protection of the health of those persons whose occupations bring them in direct contact with infected animal tissues we must rely upon education and the institution of precautionary measures.

For those persons who live on farms, or in small communities where pasteurization is not yet practiced, home pasteurization may be carried out by placing the milk in an aluminum vessel and heating it to 155° F (68.3° C), stirring constantly, then immediately setting the vessel in cold water and continuing the stirring until cool.

PROPHYLACTIC IMMUNIZATION

Kolmer, Bondi and Rule⁷³ have recently reported the apparently successful simultaneous immunization of human beings against both brucellosis and typhoid fever by administering a vaccine composed of 1,000 million heat-killed *B. typhosus* combined with similar quantities of heat-killed *Br. abortus* and of *Br. melitensis*. The vaccine was administered subcutaneously in doses of 0.5, 1 and 1 c.c. at weekly intervals. The vaccination was well borne, the mild reactions were comparable to those following typhoid-paratyphoid vaccine. About 96 per cent of the subjects developed agglutinins for *B. typhosus* and all developed both agglutinins and immune opsonin for *Br. abortus*. The serums of about 17 per cent showed some protective antibody for *Br. abortus* before immunization as compared with 79 per cent after immunization. Similarly, some protective antibody for *Br. melitensis* was present in 14 per cent of the volunteers before vaccination, after immunization all had protective antibody. Immunization with the vaccine did not appear to produce allergic cutaneous sensitization to brucellergin. These

observations would appear to justify more extended trial of this simple method of protection, particularly for those who are exposed to either typhoid or *Brucella* infection

SPECIFIC THERAPY

While there is considerable evidence that the employment of various types of serum therapy and vaccine therapy has greatly improved the outlook for most patients suffering from acute or chronic brucellosis, it is extremely difficult to evaluate the effectiveness of any form of specific therapy in a disease characterized by natural remissions and by an extremely variable symptomatology. The reported results of vaccine therapy or serum therapy run the entire gamut from pessimism to hyperenthusiasm. More extensive controlled and systematic studies on a large number of patients, carried out over a period of many years, are necessary before definite statements can be made. It would appear, however, that sufficient data have been accumulated to justify the continued and extended use of some of the specific agents

A SERUM THERAPY

Interest in serum therapy, which had waned following the earlier appearance of several unfavorable reports, has been revived by the development of a more potent anti-*Brucella* serum by Foshay^{74, 75} and his associates at the University of Cincinnati. Detoxified *Brucella* antigens are employed for the development of the antisera in goats or horses. Several favorable experiences with the Foshay serum have been recorded by other workers⁷⁶⁻⁸⁰. This type of antiserum therapy should be restricted to patients with acute or subacute brucellosis, preferably to those who have had the disease less than eight months. The dosage recommended by Foshay is as follows: for adults suffering from moderately severe to severe manifestations of the disease, the average total dose is 60 c c, given by three daily intravenous or intramuscular injections of 20 c c each or by two daily injections of 30 c c each, in unusually severe infections, 90 to 120 c c may be given in unit doses of 30 c c during a period of 48 to 72 hours, for children, a total of 20 to 30 c c may be given, either intramuscularly or subcutaneously, in daily doses of 10 c c each.

Serum therapy is not indicated in cases of chronic brucellosis of more than eight months' duration, unless sudden, severe exacerbations occur. Such abrupt relapses are usually the result of regional localizations involving the meninges, brain, spinal cord, heart valves, lungs, liver, spleen and bone marrow. In such cases, the dosage of serum would be that recommended for unusually severe infections.

B VACCINE THERAPY

It seems probable that the earlier discrepant reports of the effectiveness of vaccine therapy had their basis in a lack of standardized methods for the

preparation of the vaccines, both as regards the choice of suitable strains and the concentration of the vaccine. These difficulties appear to have been largely overcome in recent years by the development of better standards for the preparation of therapeutic vaccines.

Brucella melitensis (varieties *abortus* and *suis*) vaccine, N N R, has been widely employed and is available through the usual trade sources. This vaccine is a saline suspension of heat-killed or formalin-killed *Brucella abortus* and *suis* organisms in equal quantities. Vaccines prepared from the *melitensis* variety of the organism should be utilized only in the treatment of the relatively rare *Brucella melitensis* infections.

Experience has taught that no rigidly standardized scheme of dosage of vaccine is applicable to patients with brucellosis. Experience and good judgment are essential requisites in determining the proper dosage for each individual. The usual procedure with the commercially available vaccine is first to test for hypersensitiveness by injecting 0.05 c.c. of a 1:10 dilution of the vaccine intracutaneously. If the patient does not experience an excessive local or systemic reaction within the next 48 hours, an initial therapeutic dose of 0.25 c.c. is injected into the deep subcutaneous tissues, or preferably into the muscle. Local reactions are minimized by intramuscular injections. If no untoward reaction follows the first injection of 0.25 c.c., a second dose of 0.25 c.c. is given three days later. The dosage is then increased in increments of 0.25 c.c., at intervals of three days, until a dosage of 1 c.c. is reached. Ordinarily, two injections of 0.5 c.c. and two of 0.75 c.c. are given before the 1 c.c. dosage is attained. Five to eight injections of 1 c.c. each may then be given at three-day intervals.

If the patient is highly sensitized, it is wise to begin with intramuscular doses of 0.1 c.c., or, in rare instances of extreme sensitization, with doses of 0.1 c.c. of a 1:10 to 1:100 dilution of the vaccine, and gradually increase the dosage by 0.1 c.c. increments until a dosage of 1 c.c. is reached. If, during the course of vaccine injections an unusually severe local or systemic reaction should occur it is desirable to reduce the next dose to one-half the amount which produced the severe reaction and then cautiously and gradually increase the succeeding doses.

A series of four to six or more sharp systemic, febrile reactions, usually accompanied by a transient exacerbation of symptoms, is the goal of the treatment. Hence, only extreme local or general reactions should be avoided. Elevations of temperature to 103–105° F (39.4–40.6° C) are not uncommon within four to eight hours after the injection of vaccine. Such systemic responses may occur following the first injection of a small quantity of vaccine or may not occur until relatively large doses are given. In chronic brucellosis larger doses of the vaccine may be required; if no reaction is provoked after five or six 1 c.c. injections, the dosage may be gradually increased by 0.5 c.c. increments to 2 or 3 c.c.

While some patients who have obtained an apparently satisfactory response to vaccine therapy have had little or no thermal reaction, the most prompt and lasting results have occurred in those who have experienced several such reactions

Erythema and tenderness at the site of vaccination occur commonly for a day or two following injections. In about 5 per cent of cases, a local hard tumefaction may persist for much longer periods. In a small proportion of such cases sterile abscesses or local areas of necrosis have developed

C BRUCELLIN THERAPY

Brucellin is a fraction of *Brucella* cells obtained by growing the organism in liver broth. The bacteria-free active agent is recovered from the liver broth filtrate. This preparation was devised by I. F. Huddleson^{81, 82, 83} and may be procured at the Central Brucella Station, Michigan State College, East Lansing, Michigan.

The dosage of Brucellin must also be adjusted to suit the requirements of individual patients. After the extent of sensitiveness has been determined by the intradermal injection of 0.1 c.c. of Brucellin, the usual procedure in non-hypersensitive patients is to give repeated injections of 1 c.c. at intervals of three days until the morning and evening temperatures between the intervals of injection tend to become subnormal. Here again, one object of this form of therapy is the production of a series of four or more febrile, systemic reactions. If the duration of illness is less than 10 weeks, the likelihood of recovery following four 1 c.c. injections is greater than if the duration is longer than 10 weeks. Patients with long-continued chronic brucellosis require a larger number of injections and may require gradually increasing amounts up to 5 c.c. before satisfactory reactions are produced. In highly sensitized persons, it is advisable to start with intramuscular doses of 0.1 c.c. If there is no severe systemic reaction following this injection, each succeeding dose may ordinarily be doubled, until the larger dosage is attained.

A partially oxidized detoxified vaccine, devised by Foshay and O'Neil,⁸⁴ has been used with apparent success.⁸⁸ Much smaller doses are given subcutaneously at more frequent intervals. The few reports of results indicate the recovery rate equals that of other vaccines or Brucellin. Local or constitutional reactions do not occur with the oxidized vaccine. It has been recommended chiefly for the treatment of chronic brucellosis.

While it is difficult to evaluate the results of vaccine or Brucellin therapy, the experiences of many investigators indicate that about 60 per cent of patients with brucellosis obtain apparently complete recovery after a satisfactory course of either agent. An additional 25 per cent appear to obtain some benefit, while the remaining 15 per cent are not improved.

The contraindications to vaccine or Brucellin therapy are heart disease, renal disease, arteriosclerosis, meningeal or cerebral localizations of *Brucella* or the acute fulminating (malignant) form of the disease.

NON-SPECIFIC PROTEIN THERAPY

Injections of foreign protein substances, such as sterile skimmed milk, typhoid vaccine or typhoid-paratyphoid vaccine have been utilized^{85, 86, 87} for the production of non-specific shock reactions in the treatment of brucellosis. Erwin and Hunt^{88, 89} reported good results in 20 patients with acute and sub-acute brucellosis following the intravenous injection of killed typhoid paratyphoid organisms. The usual initial dose was 30 to 50 million killed organisms, with two to six additional injections, increasing the dosage by increments of 25 million organisms.

CHEMOTHERAPY

Neoarsphenamine, mercurochrome, acriflavine, metaphen, thionin, methylene blue, methyl violet, gentian violet and other chemical substances have been used in the treatment of brucellosis. In most instances the reports of the apparently successful use of these substances were based upon observations limited to small numbers of patients. The very length of the list argues against the specificity of any of them.

Sulfanilamide and related compounds have been heralded⁹⁰ as effective agents in the treatment of brucellosis since 1936. After the first wave of enthusiasm, usually based on short observations on relatively few patients, other reports of less favorable or entirely negative results have appeared. Blumgart and Gilligan⁹¹ analyzed the results reported in the 31 papers which appeared between 1936 and 1939. Twenty-four of the reports were concerned with only one or two patients. Of the 74 cases treated with sulfanilamide or allied compounds, there were 68 apparent recoveries and six failures. 14 of the 68 patients (20 per cent) exhibited relapse after apparent recovery. The daily dosage of sulfanilamide employed in most cases was 4 to 6 gm (60 to 90 grams) during the period of fever, with gradually diminishing dosages for three or four days after the fever abated. The administration of the drug was rarely continued for more than 12 days. Bynum⁹² reported six cases of brucellosis unsuccessfully treated with large doses of sulfanilamide. Long and Bliss⁹³ report recurrence of infection in four of five patients whose immediate response to sulfanilamide therapy was apparently quite satisfactory; in two instances *Brucella* was recovered from the blood after sulfanilamide therapy was discontinued. The writer has had similarly disappointing experiences in several cases treated with large doses of sulfanilamide, sulfapyridine or sulfathiazole, controlled by quantitative blood levels, in several instances apparent remission occurred only to be followed by relapse. *Until more extensive and extended studies are made on culturally proved cases, the value of sulfonamide therapy in cases of brucellosis must be regarded as undetermined.* In this connection it might be well to recall the fact that a temporary remission is not synonymous with cure.

ARTIFICIAL FEVER THERAPY

The observation that recovery from brucellosis often followed the induction of fever by chemical or biological agents led Prickman and Popp⁹⁴ to investigate the possible usefulness of artificial fever induced by physical means in the management of brucellosis. Each of three patients was given three artificial fever treatments, each of five hours' duration, at a rectal temperature of 105–106° F (40.6–41.1° C), all were benefited by the treatment. Zeiter⁹⁵ described a similarly favorable experience. More recently, Prickman, Bennett and Krusen⁹⁶ analyzed the results of treatment with physically induced hyperpyrexia in 21 cases of brucellosis, apparent cure resulted in 80.9 per cent of the patients. The duration of the disease prior to artificial fever therapy varied from 10 days to two and one-half years. We⁹⁷ have had similar favorable results in refractory patients who have not responded to vaccine therapy, the usual course employed by us has consisted of six fever sessions, each of three hours' duration, at a rectal temperature level of 105° F (40.6° C), given during a period of two weeks, the patients were hospitalized during the course of artificial fever treatments. Artificial fever therapy should be carried out only in properly equipped institutions by thoroughly qualified physicians and nurse-technicians.

SUMMARY AND CONCLUSIONS

1 The author's prediction of a decade ago, greeted with some skepticism at that time, that brucellosis would become recognized as a public health problem of major proportions has been fulfilled. Of the 248 cases of brucellosis studied by the author, all but 52 occurred prior to the passage of a universal pasteurization ordinance in 1931. In all but one of the 52 cases occurring during the past 10 years the patient had consumed raw milk elsewhere prior to the onset of illness, the exceptional patient was a dairy employe who drank milk before it was pasteurized.

2 The symptomatology of the acute and the chronic forms of brucellosis varies greatly. The diagnostic criteria for acute brucellosis are usually not applicable to the chronic form of the disease. There is little doubt that the chronic ambulatory form of brucellosis is widely prevalent, is often confused with other diseases, and frequently is not recognized. Many "neurasthenics" and patients with so-called "fever of unknown etiology" have been found to be victims of chronic brucellosis. Less than 10 per cent of patients with chronic brucellosis have experienced a previous acute febrile illness, compatible with a diagnosis of acute brucellosis.

3 The only diagnostic procedure by which the diagnosis of brucellosis may be established with certainty is by the cultivation and identification of the organism. The agglutination test and skin test are of considerable value in the diagnosis of acute brucellosis, but these procedures are notoriously inadequate as diagnostic aids in cases of chronic brucellosis. A positive agglutination test, particularly of low titer, and a positive skin test do not indi-

cate that the person is suffering from brucellosis at the time the tests are made Both the agglutination test and the skin test will yield entirely negative results in an appreciable number of persons from whose blood *Brucella* may be recovered

4 In our hands, the opsonocytophagic test has yielded a high proportion of inconsistent results We have found this test to be of little value as a diagnostic procedure or as a guide to therapeutic response

5 Since it is now well established that brucellosis is caused most frequently in this region by the ingestion of raw milk containing *Brucella*, the most important consideration in the control of the disease is adequate, controlled pasteurization of all milk and dairy products

6 *Brucella* vaccine therapy has produced favorable results in from 60 to 85 per cent of patients with either acute or chronic brucellosis Sulfanilamide and other sulfonamide drugs are apparently of little benefit Artificial fever therapy has yielded favorable results, particularly in those refractory patients who did not respond to vaccine therapy

BIBLIOGRAPHY

- 1 SIMPSON, W M Undulant fever (brucellosis) a clinico-pathologic study of ninety cases occurring in and about Dayton, Ohio, ANN INT MED, 1930, xvi, 238
- 2 Personal Communication from EVANS, ALICE C Pub Health Rep, 1941, lvi, 471
- 3 HARDY, A V, HUDSON, M G, and JORDAN, C F The skin as a portal of entry in *Brucella melitensis* infections, Jr Infect Dis, 1929, xlv, 271
- 4 MORALES-OTERO, P Puerto Rico Jr Pub Health and Trop Med, 1929, v, 144, 1930, vi, 3
- 5 HUGHES, M L Mediterranean, Malta, or undulant fever, 1897, Macmillan Co, London and N Y
- 6 CRAIG, C F The symptomatology and diagnosis of Malta fever, with the report of additional cases, Internat Clin 15th series, 1906, iv, 89
- 7 HARDY, A V, JORDAN, C F, BORTS, I H, and HARDY, C C Undulant fever with special reference to a study of *Brucella* infection in Iowa, Nat Inst Health Bull No 158, Dec, 1930
- 8 SIMPSON, W M, and FRAIZER, E Undulant fever report of sixty-three cases occurring in and about Dayton, Ohio, Jr Am Med Assoc, 1929, xciii, 1958
- 9 GREEN, M E, and FRYBERG, R H The incidence of brucellosis in patients with rheumatic disease, Am Jr Med Sci, 1941, cci, 495
- 10 KULOWSKI, J, and VICKER, T H Undulant (Malta) fever spondylitis, Jr Am Med Assoc, 1932, xcix, 1656
- 11 KULOWSKI, J Undulant (Malta) fever osteomyelitis and arthritis, Surg, Gynec and Obst, 1936, lxxii, 759
- 12 ARCHER, V W Undulant fever, with report of case simulating Pott's disease, South Med Jr, 1935, xxviii, 1
- 13 SNYDER, C H Spondylitis in undulant fever a report of two cases, Jr Michigan State Med Soc, 1935, xxxiv, 224
- 14 JENSEN, J P Spondylitis e Bacillo Abortus (Bang), Hospitalstidende, 1928, lxxxi, 537
- 15 LASSEN, H K Et Tilfaelde af Spondylitis paa Basis af Infektion Med Bac Abortus (Bang), Hospitalstidende, 1930, lxxxiii, 64
- 16 REDELL, G Spondylitis als Komplikation von Febris Undulans Bang, Acta Chir Scand, 1931-32, xxix, 87

- 17 ROGER, H La Spondylite Melitococcique, Presse med, 1926, cccxlii, 929
- 18 VANNUCCI, D F Sulle Spondiliti da Brucellosi, Gior d Clin Med, 1933, xv, 214
- 19 FELDMAN, W H, and OLSON, CARL, JR Spondylitis of swine associated with bacteria of the brucella group, Arch Path, 1933, xvi, 195
- 20 FELDMAN, W H, and OLSON, CARL, JR Isolation of bacteria of the brucella group in cases of spondylitis of swine An additional study, Jr Am Vet. Med Assoc, 1934, lxxxiv, 628
- 21 DE JONG, R N Central nervous system involvement in undulant fever, with report of a case and a survey of the literature, Jr Nerv and Ment Dis, 1936, lxxxiii, 430
- 22 GREEN, J Ocular manifestations in brucellosis, Arch Ophth, 1939, xxi, 51
- 23 RUTHERFORD, C W Papilledema in undulant fever, Jr Am Med Assoc, 1935, civ, 1490
- 24 RUEDEMANN, A D Uveitis, Cleveland Clinic Quart, 1941, viii, 59
- 25 AMOSS, H L, and POSTON, M A Cultivation of brucella from the stools and bile, Jr Am Med Assoc, 1930, xcvi, 482
- 26 MACQUIDDY, E L, and MARTIN, J W Cholecystitis due to *Brucella melitensis*, Nebraska Med Jr, 1934, xiv, 227
- 27 BULL, P, and GRAM, H M Cholecystitis with pure culture of *M melitensis*, Norsk Laegevidensk, 1911, ix, 1026
- 28 JOHNSON, R M Pneumonia in undulant fever report of three cases, Am Jr Med Sci, 1935, clxxxix, 483
- 29 BOGART, F B Pulmonary changes in undulant fever, South Med Jr, 1936, xxix, 1
- 30 PARETSKY, M Undulant fever, pulmonary findings simulating tuberculosis, Med Rec, 1936, cxliv, 11
- 31 LAFFERTY, R H, and PHILLIPS, C C Pulmonary changes in patients suffering from undulant fever, South Med Jr, 1937, xxx, 595
- 32 BEATTY, O A Manifestations of undulant fever in respiratory tract, Am Rev Tuberc, 1937, xxxvi, 283
- 33 SMITH, K M, and CURTIS, A C Brucellosis with endocarditis Report of a case with failure of sulfanilamide therapy, Am Jr Med Sci, 1939, cxviii, 342
- 34 DE FOREST, H P Infectious abortion of cattle as a complication of pregnancy in women, Am Jr Obst and Dis Women and Children, 1917, lxxvi, 221
- 35 LARSON, W P, and SEDGWICK, J P The complement fixation reaction of the blood of children and infants, using the *Bacillus abortus* as antigen, Am Jr Dis Child, 1913, vi, 326
- 36 SEDGWICK, J P, and LARSON, W P Further studies on the epidemic abortion reactions in children, Am Jr Dis Child, 1915, x, 197
- 37 HARBINSON, J E Undulant fever in California, ANN INT MED, 1930, iv, 484
- 38 CALDER, R M Chronic brucellosis, South Med Jr, 1939, xxxii, 451
- 39 CARPENTER, C M, and BOAK, R Isolation of *Brucella abortus* from a human fetus, Jr Am Med Assoc, 1931, xcvi, 1212
- 40 KRISTENSEN, M, and HOLM, P Bacteriological and statistical investigations on undulant fever in Denmark, Zentralbl f Bakt, 1929, cxii, 281
- 41 FREI, W Uebergang des *B abortus* Bang von Haustieren auf Menschen, Schweiz med Wchnschr, 1929, lix, 334
- 42 EVANS, A C Chronic brucellosis, Jr Am Med Assoc, 1934, ciii, 665
- 43 EVANS, A C Studies on chronic brucellosis I Introduction, Pub Health Rep, 1937, lii, 1072
- 44 EVANS, A C Studies on chronic brucellosis II Description of techniques for specific tests, Pub Health Rep, 1937, lii, 1419
- 45 POSTON, M A Studies on chronic brucellosis III Methods used in obtaining cultures, Pub Health Rep, 1938, liii, 1
- 46 ANGLE, F E Treatment of acute and chronic brucellosis (undulant fever), Jr Am Med. Assoc, 1935, cv, 939

- 47 SCOVILLE, W B The prevalence of mild *Brucella abortus* infections, Jr Am Med Assoc, 1935, cv, 1976
- 48 THAMES, E Chronic undulant fever A pathologic debility often resulting in severe nervous disorders, Med World, 1935, liii, 106, 175, 245, 306, 378
- 49 HAMMAN, L, and WAINWRIGHT, C W The diagnosis of obscure fever I The diagnosis of unexplained, long-continued low-grade fever, Bull Johns Hopkins Hosp, 1936, lviii, 109
- 50 HARRIS, H J Undulant fever (brucellosis) A supplementary report on 51 cases with observations on 120 additional cases, N Y State Jr Med, 1937, xxxvii, 1295
- 51 CAMERON, W R, and WELLS, M Undulant fever control in Washington County, Maryland, South Med Jr, 1934, xxvii, 907
- 52 GOULD, S E, and HUDDLESON, I F Diagnostic methods in undulant fever (brucellosis) with results of a survey of 8124 persons, Jr Am Med Assoc, 1937, cix, 1971
- 53 GERSH, I, and MUGRAGE, E R The incidence of positive immunologic reactions for undulant fever, Jr Lab and Clin Med, 1938, xxiii, 918
- 54 ANGLE, F E, ALGIE, W H, BAUMGARTNER, L, and LUNSFORD, W F Skin testing for brucellosis (undulant fever) in school children, ANN INT MED, 1938, xii, 495
- 55 MCGINTY, A P, and GAMBRELL, W E Chronic brucellosis, New Internat Clin, 1939, 1, 1
- 56 PINNELL, R B, and HUDDLESON, I F Chemical constitution and biological properties of the endo-antigen of the brucella group of microorganisms, Tech Bull 156, Mich State Col, Agric Exper Station, Dec, 1937
- 57 EVANS, A C The distribution of *Brucella melitensis* variety *melitensis* in the United States, Pub Health Report 52, 1937, 295
- 58 HUDDLESON, I F The differentiation of the species of the Genus *Brucella*, Tech Bull No 100, Mich State College, 1929
- 59 HUDDLESON, I F *Brucella* infections in animals and man Methods of laboratory diagnosis, Commonwealth Fund, N Y, 1934
- 60 EVANS, A C, ROBINSON, F H, and BAUMGARTNER, L Studies on chronic brucellosis IV An evaluation of the laboratory diagnostic tests, Pub Health Rep, 1938, liii, 1507
- 61 GOLDSTEIN, J D Cutaneous reactions in the diagnosis of undulant fever, Jr Clin Invest, 1934, xiii, 209
- 62 ELTON, N W Agglutination titers for *Brucella abortus* after vaccine skin tests in apparently normal persons, Arch Path, 1940, xxv, 797
- 63 HUDDLESON, I F, JOHNSON, H W, and HAMANN, E E A study of the opsonocytophagic power of the blood and allergic skin reaction in brucella infection and immunity in man, Am Jr Pub Health, 1933, xxiii, 917
- 64 KELLER, A E, PHARRIS, C, and GAUB, W H Diagnosis of undulant fever The opsonocytophagic, allergic and agglutination reactions, Jr Am Med Assoc, 1936, cvii, 1369
- 65 KELLER, A E, PHARRIS, C, and GAUB, W H Undulant fever comparative value of certain diagnostic tests, South Med Jr, 1938, xxxi, 1
- 66 MORALES-OTFRO, P, and GONZALEZ, L M Allergy in brucella infections, Proc Soc Exper Biol and Med, 1939, xl, 100
- 67 FOSHAY, LEE: The laboratory diagnosis of undulant fever, Am Jr Clin Path, 1940, x, 176
- 68 FOSHAY, LEE Chapter on brucellosis Modern medical therapy in general practice, 1940, Williams and Wilkins Co, Baltimore, pp 1305-1339
- 69 CALDER, R M, STEVEN, C, and BAKER, L Blood studies in brucellosis, Jr Am Med Assoc, 1939, cxii, 1893
- 70 MURRAY, C, MCNUTT, S H, and PURWIN, P The effect of pasteurization upon *Br. melitensis* var *suis*, Jr Am Vet Med Assoc, 1932, xxxiii, 336
- 71 BOAK, R., and CARPENTER, C M Thermal death point of *Brucella abortus* in milk, Jr Infect. Dis, 1923, xliii, 327

- 72 ZWICK, and WEDEMAN Cited by Boak and Carpenter ⁷¹
- 73 KOLMER, J A, BONDI, A, JR, and RULE, A M Results of active immunization of human beings with a mixed heat-killed vaccine of *Bacillus typhosus*, *Brucella abortus* and *Brucella melitensis*, Jr Infect Dis, 1940, lxxvii, 258
- 74 WHERRY, W B, O'NEIL, A E, and FOSHAY, L Brucellosis in man treatment with a new antiserum, Am Jr Trop Med, 1935, xv, 415
- 75 FOSHAY, L Serum therapy in human brucellosis (Abstract), Jr Bacteriol, 1937, xxxiii, 42
- 76 MILLER, J L Undulant fever, ANN INT MED, 1934, viii, 570
- 77 BANNICK, E G, and MAGATH, T B Case of brucellosis treated with antiserum, Proc Staff Meet Mayo Clin, 1936, xi, 17
- 78 CASEY, J F Brucellosis (undulant fever) Interesting and important facts about the disease with the report of a severe case occurring in a Boston physician, New Eng Jr Med, 1936, ccxv, 1282
- 79 WOODWARD, L R Brucellosis, Jr Iowa State Med Soc, 1937, xxvii, 609
- 80 NEWMAN, H G Undulant fever, Jr Missouri State Med Assoc, 1938, xxxv, 398
- 81 HUDDLESON, I F, JOHNSON, H W, and BEATTIE, C F Studies in brucella infection A report of 100 cases treated with brucellin, Bull 149, Agric. Exper Sta, Mich State College, May, 1936
- 82 HUDDLESON, I F, and JOHNSON, H W Brucellin, a possible specific for undulant fever in man, Am Jr Trop Med, 1933, xiii, 485
- 83 HUDDLESON, I F Brucellosis Causes, sources of infection, clinical diagnosis, laboratory diagnosis, treatment, Bull Central Brucella Station, Mich State College, 1938
- 84 O'NEIL, A E Preliminary note on the treatment of undulant fever in man with detoxified vaccine and with antiserum, Ohio State Med Jr, 1933, xxi, 438
- 85 BUDTZ-OLSEN, J Undulant fever treatment with typhoid vaccine, Ugeskr f Laeger, 1930, xcii, 596
- 86 MILLER, S Protein shock therapy in undulant fever, Lancet, 1933, i, 1177
- 87 MANSON-BAHR, P Undulant fever of the abortus type treated by protein shock, Lancet, 1933, i, 1178
- 88 ERWIN, C E, and HUNT, H F The diagnosis and treatment of undulant fever, Jr Am Med Assoc, 1937, cix, 1966
- 89 ERWIN, C E, HUNT, H F, and NILES, J S, JR Foreign protein therapy II Treatment of undulant fever by the intravenous injection of killed typhoid-paratyphoid A and paratyphoid B bacilli, Am Jr Med Sci, 1936, cxcii, 234
- 90 GROUES, P Sur quelques cas de melitococcie traitée par le rubiazol seul ou associe a des agents thérapeutiques spécifiques de l'affection, Lyon méd, 1936, clviii, 615
- THEVENET, V Un cas de melitococcie traitée par le rubiazol (per os) Terminaison favorable relativement rapide de la maladie, Lyon med, 1936, clviii, 668
- BERGER, W, and SCHNETZ, H Ein Behandlungserfolg bei Morbus Bang mit Prontosil, Med Klin, 1937, xxxiii, 594
- SUCHIER, W Zur Behandlung der Bangschen Krankheit, Fortschr d Therap, 1937, xiii, 305
- BETHOUX, L, GOURDON, E, and ROCHERY, J Melitococcie traitée par le chlorhydrate de sulfamino-chrysoidine, amelioration clinique, persistance des germes dans le sang, Bull et mem Soc. med d hôp de Paris, 3rd series, 1937, 678
- AHRINGSMANN, H Heilung der Bangschen Krankheit durch Prontosil, München med Wchnschr, 1937, lxxiv, 1778
- BÉTHOUX, L, GOUDON, E, and ROCHERY, J Fievre ondulante guérie cliniquement et bacteriologiquement par l'emploi de derives sulfamides non azoïques, Bull et mem Soc. med d hôp de Paris, 3rd series, 1937, 1297
- BEVAN, LL E Abortus fever some notes from Southern Rhodesia Treatment of a human case with prosecticne, Jr Comp Path and Therap, 1937, i, 338
- LLOYD, J H Sulfonamide-P in *Brucella abortus* infection, Brit Med Jr, 1938, i, 145

- RICHARDSON, L A Infection with *Brucella abortus* treated with prontosil, Lancet, 1928, 1, 495
- FRANCIS, A E Sulfanilamide in the treatment of undulant fever, Lancet, 1938, 1, 496
- STERN, R L, and BLAKE, K W Undulant fever, its treatment with sulfanilamide, Jr Am Med Assoc, 1938, cx, 1550
- MANSON-BEHR, P The action of sulphanilamide on *Brucella abortus* infections, Practitioner, 1938, cxl, 740
- HALL, L T, and DUNLAP, R L Report of a case of *Brucella abortus* infection treated with sulfanilamide, Nebraska State Med Jr, 1938, xxiii, 252
- WELCH, H, WENTWORTH, J A, and MICKLE, F L The use of sulfanilamide in the diagnosis and treatment of brucellosis, Jr Am Med Assoc, 1938, cxl, 226
- SHEPPE, W M Sulfanilamide in the treatment of undulant fever, Jr Chemotherapy, 1938, xv, 38
- BLUMGART, H L Recovery of a patient with undulant fever treated with sulfanilamide, Jr Am Med Assoc, 1938, cxl, 521
- PETZETAKIS, M D Abortivebehandlung des Maltafiebers durch Prontosil, Deutsch med Wchnschr, 1938, lxiv, 1147
- PUNCH, A L Undulant fever treated with prontosil, Lancet, 1938, 11, 429
- THOMSON, A P Treatment of *Brucella abortus* infection with Fouadin and Prontosil, Brit Med Jr, 1938, 11, 884
- FRASER, R H, WHITE, F D, and PERRIN, M B A résumé on undulant fever the use of prontosil and prontosil (report of two cases), Canad Med Assoc Jr, 1938, xxxix, 455
- MATTHEWS, N *Brucella abortus* infection treated by sulfanilamide, Brit Med Jr, 1938, 1, 483
- PAGE, W. A ; *Brucella abortus* infection treated by sulfanilamide, Brit. Med Jr, 1938, 1, 594
- TRAUT, E F, and LOGAN, C E Undulant fever treated with sulfanilamide, Jr Am Med Assoc, 1938, cxl, 1092
- NEUMANN, C Z Treatment of undulant fever with Prontosil, Brit Med Jr, 1938, 11, 342
- TOONE, E C, JR, and JENKINS, A M Undulant fever (brucellosis) treated with sulfanilamide Report of case with recovery, South Med Jr, 1938, xxxi, 478
- HADEN, R L The treatment of undulant fever with sulfanilamide Report of a case, Cleveland Clin Quart, 1938, v, 24
- LIVINGSTON, A E Undulant fever treated with sulfanilamide, Rocky Mountain Med Jr, 1938, xxxv, 787
- BARTFELS, E C Sulfanilamide in undulant fever, New England Jr Med, 1938, ccxiv, 988
- GAFFNEY, M. Report of five cases of *Brucella abortus* infection, Brit Med Jr, 1938, 11, 885
- 91 BLUMGART, H L, and GILLIGAN, S R The treatment of undulant fever with sulfanilamide and related compounds, Med Clin N Am, 1939, xxiii, 1193
- 92 BYNUM, W T Recurrences of undulant fever (brucellosis) following the administration of sulfanilamide, Jr Am Med Assoc, 1939, cxii, 835
- 93 LONG, P H, and BRISS, E A The clinical and experimental use of sulfanilamide, sulfa-pyridine and allied compounds, 1939, Macmillan Co, N Y, 209
- 94 PRICKMAN, L E, and POPP, W C Treatment of brucellosis by hyperpyrexia induced by the Simpson-Kettering hypertherm, Proc Staff Meet Mayo Clin, 1936, xi, 506
- 95 ZEITER, W J Treatment of undulant fever by artificial fever therapy Report of a case, Cleveland Clin Quart, 1937, iv, 309
- 96 PRICKMAN, L E, BENNETT, R L, and KRUSEN, F H Treatment of brucellosis by physically induced hyperpyrexia, Proc Staff Meet Mayo Clin, 1938, xiii, 321
- 97 SIMPSON, W M. Discussion of paper by EDWIN, C E, and HUNT, H F The diagnosis and treatment of undulant fever, Jr Am Med Assoc, 1937, cx, 1970

THE SULFONAMIDE THERAPY OF STAPHYLOCOCCAL SEPTICEMIA *

By ROBERT G TORREY,† F A C P , *Philadelphia, Pennsylvania*, L A JULIANELLE, *St Louis, Missouri*, and H G McNAMEE, *Philadelphia*

INTRODUCTION

THE history of medicine probably contains no parallel example of the generalized acceptance and popularity of a treatment as that of the sulfonamide derivatives. While there can be little question of the efficacy of these drugs in certain infections, it is becoming increasingly apparent from the slowly accumulating reports of more conservative observers, that the exaggerated faith in their panaceal capacities does not appear to be justified, as, indeed, recent critical reviews illustrate¹⁻³. Among the different communications devoted to sulfonamide therapy, a number of scattered reports have dealt with the successful treatment of staphylococcal septicemia. Consisting to a great extent of individual case histories, scanty in detail and relevant information, the reports are difficult to appraise in regard to the actual value of the sulfonamides in this form of infection. This becomes even more difficult when it is realized that while successes are reported, failures usually are not, thus presenting the reader with a one-sided point-of-view.

While studying the effect of an experimental, antibacterial serum⁴ on staphylococcal septicemia, there have been referred from time to time to the present writers patients in whom the sulfonamide drugs were frank failures in checking the course of infection. With the number of such patients mounting steadily, a feeling of doubt was created regarding the degree of effectiveness of any of the sulfonamides thus far introduced to control severe staphylococcal infection. It was decided, therefore, to analyze the data on hand in order to ascertain the exact conditions and results of the drug therapy. It must be said in fairness that the criticism applied above to the one-sided reporting of successful treatment is equally tenable in this instance, since the cases to be described herewith represent unsuccessful treatment, only. In justification of this position, however, it must be remembered that *genuine* staphylococcal septicemia is not common, so that the relatively large number of patients, as will be reported below, may be a better indication of the probable outcome awaiting the treatment of such infection with these drugs than appears on the surface.

* Received for publication April 9, 1941

From The Department of Medicine, Women's Medical College, Philadelphia, the Department of Ophthalmology, Washington University School of Medicine, St Louis, and the Philadelphia General Hospital, Philadelphia

A grant from the Commonwealth Fund of New York (to L. A. J.) aided in the conduct of this study.

† Dr Robert G Torrey died before this manuscript was completed, so that the responsibility for the opinions expressed must fall entirely upon the junior authors.

REVIEW OF THE LITERATURE

Before considering the statistical evidence in the hands of the writers, it may be of value to review briefly the experience of preceding workers. That presentation of their results may be simplified, the available data derived from 27 different references have been arranged in tabular form (table 1)

TABLE I
Collected Statistics on Effect of Sulfonamides in Staphylococcal Septicemia

Investigators	Drug Studied	Number of Patients	
		Treated	Recovered
Foerster ⁵	Prontosil	1	1
Mitchell ⁶	Uleron	3	3
Colebrook and Kenny ⁷	Sulfanilamide	3	2
Mendell ⁸	"	3	0
Thornhill et al ⁹	"	2	2
Blake and Haviland ¹⁰	Sulfapyridine	5	0
Fenton and Hodgkiss ¹¹	"	1	1
Galewski and Stannus ¹²	"	1	1
Goldberg and Sachs ¹³	"	2	2
Hartmann et al ¹⁴	"	2	2
Long ¹⁵	"	5	3?
			(rapid sterilization)
Martin and Bryan ¹⁶	"	5	4
O'Brien and McCarthy ¹⁷	"	1	1
Spink, Hansen, and Paine ¹⁸	"	10	6
Wade ¹⁹	"	1	1
Carroll et al ²⁰	Sulfamethylthiazole	3	3
Hartmann ²¹	"	8	3
Herrell and Brown ²²	"	1	1
Weisman and Russell ²³	"	2	2
Carey ²⁴	Sulfathiazole	6	3
Fitch ²⁵	"	1	1
Keliher and Carlan ²⁶	"	1	1
Rammelkamp and Keefer ²⁷	"	7	3
Scott ²⁸	"	1	1
Spink, Hansen, and Paine ¹⁸	"	19	18
Stirling ²⁹	"	1	1
Abramson and Flacks ³⁰	Different compounds	6	2
Herrell and Brown ³¹	"	27	15
Totals		128	83

If the figures are accepted at their face value, it is seen that a total of 128 cases are recorded as having been treated with one or another of the sulfonamide compounds, and of these 83 recovered, presumably because of the drug therapy, thus demonstrating an effective rate of these compounds of close to 65 per cent. This is obviously an impressive ratio, approximately reversing the usual figures for fatality and survival in staphylococcal septicemia. However desirable it may be, it is impossible to attempt further analysis, since with few notable exceptions,^{10, 14, 21, 27, 31} the publications summarized lack sufficient information for the purpose. It is nevertheless interesting that in a number of instances, diagnosis of septicemia was based on a single, positive

blood culture, and in one case, only one of several blood cultures yielded growth, and then a single colony of *Staphylococcus*. The optimum blood concentration of the drug attained varies with the different reports from 3 mg (27) to 6 mg¹⁸ to 20 mg³¹ per 100 c c of blood. While the number of cases is too few for statistical evaluation, the impression gathered is that sulfathiazole shows the maximum effect, this impression strengthened by the high degree of success with this drug reported by Spink, Hansen, and Paine¹⁸. The majority of the publications represents small numbers of patients, even though in the aggregate, a considerable figure is reached. Unfortunately, however, it is more than likely that for the most part the reports were made primarily to point out the therapeutic effectiveness of the drugs. Failures experienced by other observers, on the other hand, are not to be found in print, if it is fair to judge from the number of personal, unsolicited communications received by the writers from various physicians in this country. Consequently, while the degree of efficiency as represented in the literature is undoubtedly high and gratifying, it must be remembered that the picture is incomplete.

OBSERVATIONS AND RESULTS

In preparing the data of the present communication for analysis, it was found convenient to tabulate the patients under the particular drug employed. Diagnosis of septicemia was based on several daily blood cultures yielding staphylococci, and in most cases the additional technic was incorporated of plating measured amounts of blood to determine the number of colonies per c c of blood. The significance of the culture was subsequently established by the fermentation of mannite³² and by the extraction and precipitation of the specific carbohydrate (Type A) elaborated by the bacterial cell³³. The sulfonamide drugs were given as early as possible and the dosages given, while variable, were well within the usual limits. Chemotherapy was then continued to a point where it was decided by the physician in charge that the chemotherapy was a failure, when one of the present writers was called upon for consultation. In certain patients some other form of treatment was substituted for the drug, but in such instances, the subsequent method of treatment has been tabulated only when the patient survived, or it was possible to continue the substituted treatment for a reasonable length of time to establish its effect (i e., for at least 48 to 60 hours). It did not seem fair to include any treatment given for less than the designated period, because it was obvious that in such cases the condition was already hopeless before therapy was instituted. In addition to the drug therapy, each patient was given whatever surgical care and supportive treatment was indicated during the course of the disease.

In table 2, will be found the data bearing on the treatment of staphylococcal septicemia with sulfanilamide. It will be seen that 19 patients with septicemia arising from a variety of localized conditions were given the drug

TABLE II
Effect of Sulfanilamide on Staphylococcal Septicemia

Patient	Age	Sex	Diagnosis	Drug Treatment			Subsequent Specific Treatment	Ultimate Outcome	Comments
				Day Started	Duration (Days)	Effect			
M C 1	37 yrs	F	Furunculosis Pneumonia Septicemia	8th	21	none	Phage	Died	Phage and drug treatment concurrent
C W 4	18 mos	F	Primary focus ? Septicemia	3rd	15	none		Died	
V V 5	7 mos	F	Septicemia	2nd	10	none		Died	
M D 8	35 yrs	F	Furunculosis Renal abscesses Septicemia	1st	6	none	Antitoxin then Antibacterial serum	Recovered	Drug started first day of septicemia not furunculosis
D K 12	4 yrs	F	Tonsillitis Osteo l tibia Septicemia	2nd	6	none	Antibacterial serum	Recovered	
C S 13	25 yrs	M	Cellulitis-face Pneumonia Septicemia	2nd	10	none	Antibacterial serum	Recovered	
A M 16	63 yrs	M	Infected nose Pneumonia Septicemia	3rd	8	none	Antitoxin 7 days	Died	
W N 25	21 yrs	M	Infected finger Extension along arm Pneumonia Septicemia	3rd	4	none		Died	
V C 26	24 yrs	F	Self abortion Osteo l hip Pneumonia Septicemia	3rd	4	none	Antibacterial serum	Recovered	
M A 27	10 yrs	M	"Scarlet fever" Pneumonia Pleurisy Septicemia	3rd	8	none		Died	
D R 31	26 yrs	F	Sore throat Cervical adenopathy Pneumonia Septicemia	9th	5	none		Died	Drug started 1st day of septicemia, discontinued because of toxic reactions
P V 35	57 yrs	M	Infected thigh Cellulitis Thrombophlebitis Septicemia	7th	5	none	Antibacterial serum	Died	
H J 46	44 yrs	M	Cellulitis l foot and leg Pneumonia Pleurisy Septicemia	1st	5	none	Antibacterial serum	Died	
R W 63	5 yrs	M	Osteo l knee Septicemia	2nd	6	none	Antibacterial serum	Recovered	
S B 75	6 yrs	F	Cellulitis-face Sinus thrombosis Bacterial meningitis Septicemia	3rd	2	none		Died	
I B 80	9 yrs	M	Osteo foot Septicemia Endocarditis	2nd	6	none		Died	
M-C 5	14 yrs	F	Osteo rib Pleurisy Septicemia	3	10	?		Recovered	Septicemia questionable (See text)
M-C 12	47 yrs	F	Diabetes Furunculosis Septicemia	1st	10	none		Died	
J N 95	24 yrs	F	Post-abort infection Septicemia	1st	7	none	Antibacterial serum	Died	Endocarditis obvious after serum therapy started

from the first to the ninth day of illness, and this therapy was continued for variable periods up to 21 days. In each case but one (M-C 5) sulfanilamide had failed to check infection. This was particularly striking in certain patients (M D 8, D K 12, D R 31, H J 48, M-C 12), since the septicemia in these cases developed as a secondary complication while the drug was being administered to restrain what was at the time a purely localized infection. With sulfanilamide exerting no apparent benefit, recourse was had to other therapeutic agents as specified: bacteriophage in one, antitoxin in two, antibacterial serum in eight. The only success obtained was with the latter in that of the eight, five recovered and three died. In the remaining nine cases, reported as having no subsequent specific treatment, some actually had no other treatment or the treatment was not continued sufficiently long to consider the attempt a fair trial. In one patient (M-C 5) recovery occurred following 10 days of treatment with sulfanilamide. This case, however, was considered as a transient bacteremia, because of 10 consecutive daily cultures, the first, fourth, and eighth were positive with never more than three colonies per c c of blood, and the remaining cultures yielded no growth. The indications are, therefore, that in this group of 19 patients treated with sulfanilamide, the drug certainly did not offer any protection against the infection in 18 cases, and possibly not even in the nineteenth.

The data relating to the use of sulfapyridine will be found in table 3. Analysis reveals that 12 individuals were treated with this derivative, the treatment being started on the second to the seventh day of illness and lasting from four to 28 days. In this series also are to be found examples of septicemia developing during drug treatment (M S 28, R S 45). Of the 12 patients, one was later given antitoxin and died, while seven received antibacterial serum with four survivals and three deaths. A careful review of the individual clinical records leaves no alternative but that sulfapyridine accomplished little, if anything, in this group of patients.

Possibly due to the early withdrawal of sulfamethylthiazole from circulation, the present records include only two examples of treatment with this drug (table 4). Both patients received the drug as the only specific measure. One (M B 1) starting with a localized infection developed septicemia during administration of the drug, while the other was an instance of rapid, fulminating infection. Both alike were unaffected by the treatment.

As will be seen in table 5, 20 patients were treated with sulfathiazole. The time of starting the drug varied from the first to the seventh day of illness, and the duration of treatment varied from four to 29 days. Two patients subsequently received antitoxin and both died. Antibacterial serum was substituted for the drug in nine patients, and of these seven recovered. The remaining nine, representing drug treatment alone or supplemented with some other specific agent at too late a stage to help, all died.

Table 6 represents patients treated with a combination of sulfonamide compounds. Thus, three received sulfanilamide and sulfapyridine, three

TABLE III
Effect of Sulfapyridine on Staphylococcal Septicemia

Patient	Age	Sex	Diagnosis	Drug Treatment			Subsequent Specific Treatment	Ultimate Outcome	Comments
				Day Started	Duration (Days)	Effect			
B O 24	23 yrs	F	Pneumonia Septicemia Meningitis Endocarditis	3rd	7	none		Died	
M S 28	6 yrs	F	Pneumonia Pleurisy Septicemia	3rd	5	none	Antibacterial serum	Recovered	
A R 29	35 yrs	M	Pneumonia Septicemia	2nd	10	none		Died	
S S 30	49 yrs	F	Infected needle prick Pneumonia Septicemia	2nd	22	none	Antibacterial serum	Died	
D P 42	11 yrs	M	Osteo l shoulder Pneumonia Septicemia	4th	6	none	Antibacterial serum	Recovered	
C H 44	28 yrs	M	Infected pimple Septicemia	2nd	14	none		Died	
R S 45	12 yrs	M	Osteo Septicemia	3rd	5	none	Antibacterial serum	Recovered	
L B 49	22 yrs	F	Carbuncle l shoulder Pneumonia Septicemia	2nd	6	none	Antibacterial serum	Died	
D S 51	13 yrs	F	Pneumonia Septicemia Endocarditis	7th	10	none	Antibacterial serum	Died	Serum administered after endocarditis
M M 66	12 yrs	F	Osteo Septicemia	3rd	6	none	Antibacterial serum	Recovered	
M S 78	13 yrs	M	Osteo r tibia Septicemia	6th	28	none	Antitoxin	Died	
M -C 73	17 yrs	F	Abscess site of thoracentesis Septicemia	2nd	4	none		Died	

TABLE IV
Effect of Sulfamethylthiazole on Staphylococcal Septicemia

Patient	Age	Sex	Diagnosis	Drug Treatment			Subsequent Specific Treatment	Ultimate Outcome	Comments
				Day Started	Duration (Days)	Effect			
M B 1	37 yrs	M	G U infection from catheter Septicemia	2nd	16	none	none	Died	
M B 2	40 yrs	F	Diabetes Furunculosis Septicemia	3rd	12	none	none	Died	

TABLE V
Effect of Sulfathiazole on Staphylococcal Septicemia

Patient	Age	Sex	Diagnosis	Drug Treatment			Subsequent Specific Treatment	Ultimate Outcome	Comments
				Day Started	Duration (Days)	Effect			
B B 55	32 yrs	F	Pneumonia Septicemia	7th	15	none		Died	
L C 58	11 yrs	F	Osteo l tibia and r ulna Septicemia Endocarditis	4th	5	none	Antibacterial serum	Died	Serum given after endocarditis was obvious
G O 64			Osteo Septicemia	5th	6	none	Antibacterial serum	Re-covered	
S T 69	60 yrs	M	Diabetes Carbuncle neck Pneumonia Septicemia	6th	Intermittent over 29 days	none		Died	
W H 72	20 mos	M	Osteo Septicemia	2nd	24	none	Antibacterial serum	Re-covered	
T N 73	21 mos	M	Infected foot Septicemia	4th	9	none	Antibacterial serum	Re-covered	
M V 76	23 yrs	F	Infected toe Septicemia Endocarditis	6th	6	none	Antibacterial serum	Died	Serum given after endocarditis was obvious
P B 77	3 yrs	M	Osteo Septicemia	3rd	8	none	Antibacterial serum	Re-covered	
F B 84	37 yrs	F	Perinephritic abscess Pneumonia Septicemia	?	12	none	Antibacterial serum	Re-covered	
L S 87	38 yrs	M	Gluteal abscess Septicemia	2nd	8	none		Died	
M O 88	40 yrs	M	Infected finger Pneumonia Pleurisy Septicemia	3rd	10	none		Died	
W-MC 1	4 yrs	M	Osteo Septicemia	4th	20	none	Antitoxin	Died	
W-BC 2	16 mos	M	Osteo Septicemia	4th	12	none	Antitoxin	Died	
P E	20 mos	M	Primary focus? Septicemia Pericarditis	3rd	16	none		Died	
D F	6 yrs	F	Osteo Septicemia	?	24	none		Died	
D O	30 yrs	M	Cellulitis Septicemia Multiple metastatic abscesses	?	20	none		Died	
J S 89	7 mos	F	Osteo Convulsions Septicemia Metastatic abscess Agranulocytosis	6th	4	none		Died	Rapid fulminating infection
J H 91	6 mos	F	Pneumonia following inhalation of foreign body Septicemia	5th	5	none		Died	Rapid fulminating infection
M M 94	?	F	Post-operative pneumonia Septicemia	1st	6	none	Antibacterial serum	Re-covered	
E E 96	32 yrs	F	Primary pneumonia Septicemia	2nd	11	none	Antibacterial serum	Re-covered	

TABLE VI
Effect of Combined Sulfonamide Drugs on Staphylococcal Septicemia
A Sulfanilamide and Sulfapyridine

Patient	Age	Sex	Diagnosis	Drug Treatment			Subsequent Specific Treatment	Ultimate Outcome	Comments
				Day Started	Duration (Days)	Effect			
J T 39	9 yrs	F	Osteo r foot, r scapula, l ulna, l fibula Septicemia	3rd	Sulfanilamide-4 Sulfapyridine-4	none	Antitoxin 4 days, then antibacterial serum	Re- covered	
F B 43	15 yrs	M	Osteo Septicemia	6th	Sulfanilamide-12 Sulfapyridine	none	Phage anti- toxin, then antibacterial serum	Re- covered	Sulfapyridine was given intermittently over a period of 8 weeks
M M	15 yrs	M	Osteo skull Septicemia	4th	Sulfanilamide-3 Sulfapyridine-5	none	Antibacterial serum	Re- covered	

B Sulfanilamide and Sulfathiazole

M B 57	11 yrs	F	Osteo r hip Septicemia Pericarditis	2nd	Sulfanilamide-2 Sulfathiazole-15	none	Antibacterial serum	Died	Serum used after pericarditis was obvious
C K 70	3 wks	F	Gingival abscess Osteo r tibia Septicemia	4th	Sulfanilamide-3 Sulfathiazole-8	none		Died	
A T 85	15 yrs	M	Osteo l tibia Septicemia	2nd	Sulfanilamide-2 Sulfathiazole-4	none	Antibacterial serum	Re- covered	

C Sulfapyridine and Sulfathiazole

J P 71	8 yrs	M	Abscess r shoulder Septicemia	3rd	Sulfapyridine-2 Sulfathiazole-2	none		Died	
--------	-------	---	-------------------------------------	-----	------------------------------------	------	--	------	--

D Sulfamethylthiazole and Sulfathiazole

D K 56	5 yrs	F	Paronychia r thumb Septicemia Pericarditis Osteo r femur	5th	8	none	Phage then antibacterial serum	Died	Serum used after pericarditis was obvious
J H	16 yrs	F	Osteo l hip Septicemia	2	12	none		Died	
J C	37 yrs	F	Nephritic abscess Septicemia	5th	6	none		Died	

sulfanilamide and sulfathiazole, one sulfapyridine and sulfathiazole, and three, sulfamethylthiazole and sulfathiazole. The evidence is similar to that of the preceding tables. After unsuccessful trial with the combined drugs, three of the 10 patients were subsequently treated with antibacterial serum and two recovered, three were given combinations of phage, antitoxin, and

antibacterial serum and one recovered, the remaining four, with no other treatment, all died

Thus, then, if all the data are summarized (table 7) it is seen that 62 patients were treated with different sulfonamide derivatives. Except for the doubtful case referred to above (M-C 5), there appears to be little choice in the different derivatives used and little evidence for accepting this form of

TABLE VII
Summary of Sulfonamide Treatment of Staphylococcal Septicemia

Sulfonamide Drug Used	No of Patients	Effect of Drug	Subsequent Specific Treatment	Ultimate Outcome
Sulfanilamide	18	none	Phage 1 Antitoxin 1 Antibacterial serum 8 *No other treatment 8	Died Died 5 Recovered, 3 died 7 Died, 1 recovered?
Sulfapyridine	12	none	Antitoxin 1 Antibacterial serum 7 No other treatment 4	Died 4 Recovered, 3 died 4 Died
Sulfamethylthiazole	2	none	No other treatment 2	2 Died
Sulfathiazole	20	none	Antitoxin 2 Antibacterial serum 9 No other treatment 9	2 Died 7 Recovered, 2 died 9 Died
Combined drugs	10	none	Antibacterial serum 3 Antitoxin followed by antibacterial serum 1 Phage followed by antibacterial serum 1 Phage followed by antitoxin, then by antibacterial serum 1 No other treatment 4	2 Recovered, 1 died Died Died Recovered 4 Died
Grand totals	62	none	Phage 1 Antitoxin 4 Antibacterial serum 27 Combined biological agents plus antibacterial serum 3 No other treatment 27	Died 4 Died 18 Recovered, 9 died 1 Recovered, 2 died 1 Recovered?, 26 died

* This implies that other specific treatment was not attempted, or was of too short duration to be significant. All patients received both whatever surgical care was indicated and the usual supportive measures.

chemotherapy as a strikingly specific treatment for staphylococcal septicemia. For example, of the 62 patients, 42 eventually died, the remaining 20 surviving, according to the writers' interpretation, because of other therapy. If the objection be made, however, that the sulfonamides contributed to the recovery of the surviving patients, thereby discounting completely the later treatment, the mortality rate on this basis still attains a figure of over 67 per cent. Such a result, it must be admitted, at best only matches the "average"

rate, and therefore, shows no improvement over the usual non-specific measures employed in the past

There is no particular point to be gained at the present time by discussing the effect of the subsequent, specific measures adopted This is part of an-

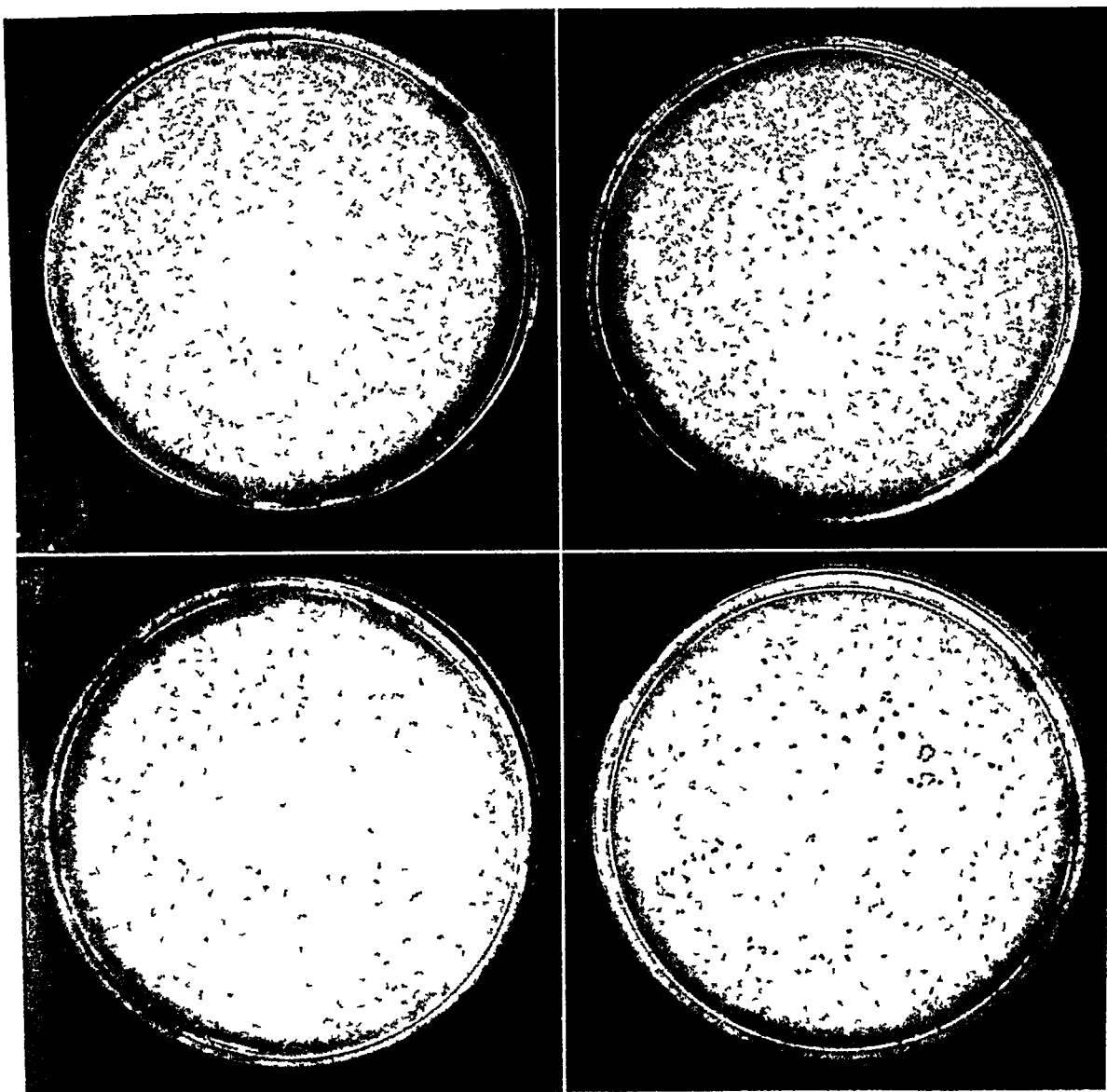


FIG 1a Effect of sodium sulfathiazole (30 per cent) on culture of *Staph aureus* 1/20,000 c.c of culture plated before and after mixing Upper left, before Upper right, 2 min after Lower left, 15 min after Lower right, 60 min after

other investigation to be reported later For the time being, it may suffice to say that they have been included to keep the records complete, and to demonstrate that, in the patients surviving, some treatment other than the sulfonamides was more probably responsible for recovery

In this connection, it is of interest to describe an experiment repeated on several occasions to determine the *in vitro* effect of the sulfonamides on *Staphylococcus* For this purpose the thiazole compound was particularly

studied, since by reputation, at least, it appears to be the most effective in such infections. Because of the high solubility of its sodium salts, it was used in this form. Saturated solutions (approximately 60 per cent) were used entirely, and on subsequent mixing with equal volumes of broth cul-

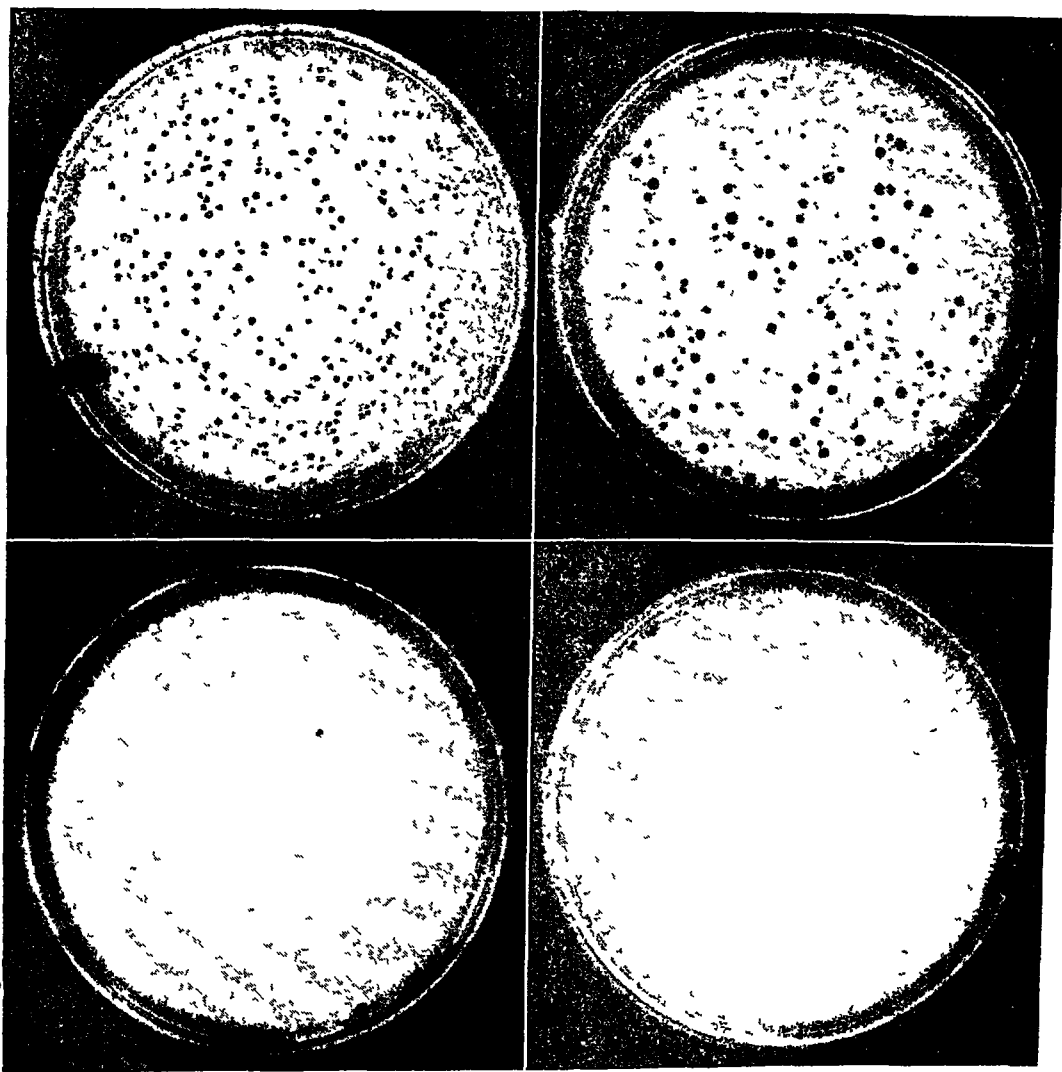


FIG 1b Effect of sodium sulfathiazole (30 per cent) on culture of *B. coli* 1/20,000 c.c. of culture plated before and after mixing. Upper left, before. Upper right, 2 min after. Lower left, 15 min after. Lower right, 60 min after.

ture, the concentration was accordingly reduced to 30 per cent, and the alkalinity measured from pH 10.5 to pH 11.0.

Upon mixing equal volumes of solution and culture, there was an immediate, curious effect, later recognized as an optical illusion, but originally interpreted as a solubility effect (i.e., that staphylococci are soluble in 30 per cent sodium sulfathiazole). Subsequent study revealed that actually the organisms are not dissolved, but that possibly the drug causes a change in

the refractive index of the bacteria, or the menstruum, thus giving the false appearance of a solution, an opinion, however, still remaining to be proved

Young broth cultures (8 to 12 hours), then, were mixed in equal volumes with the sodium salt as indicated, and at specified intervals cultures were plated in meat infusion agar to determine the effect of the drug on viability of the *Staphylococcus*. Thus, cultures were made with 1/20,000 c c before adding the drug and at two, 15, and 60 minutes following mixing. In order to illustrate the results observed, photographs were made after 24 hour incubation of the cultures, and these are submitted in the accompanying plate. Merely a glance suffices to demonstrate that no appreciable effect was noticeable under the conditions stated. In other words, at a concentration, approximating five thousand times that in the blood of treated patients (6 mg per 100 c c) and for exposures up to one hour, sodium sulfathiazole apparently altered very little, if any, the original number of staphylococci. When the exposure was continued for 20 hours, there was a decrease of about 80 per cent to 90 per cent in cultivable organisms, but this was probably due to the high alkalinity effecting dissolution of the bacterial cells. Comparable results were obtained with three different strains, each isolated from blood cultures during septicemia, and from patients not treated with sulfonamide derivatives.

For purposes of control, similar experiments were conducted with two different strains of recently isolated *B. coli*. Within two minutes, there was a remarkable diminution in the number of colon organisms, and in 15 minutes, sterilization was complete. Parenthetically, it is interesting to add that this bacterium did not give the "solubility" phenomenon noted above. The contrast in the behavior of the drug on the two species, and the implications arising therefrom are too obvious to require comment.

DISCUSSION

Reconciliation of divergent observations is usually difficult, and more often than not, both unsatisfactory and inconclusive. This should not justify, however, either ignoring completely or dismissing casually the presence of such a situation. Admitting at the outset, that those patients benefited by sulfonamide therapy were not referred to the present writers, but only those in whom the treatment was ineffectual, it is nevertheless clear that the results reported here cast some doubt, at least, on the high percentage of effectiveness reported by other workers. Perhaps of foremost importance in this discussion is the evidence on which the diagnosis of septicemia is based. As far as blood cultures per se go, growth of staphylococci may imply either transient passage of bacteria through the circulation (i.e., bacteremia), or their prolonged presence with frequently increase in numbers (i.e., septicemia). Consequently, repeated blood cultures, with preferably an estimation of the number of colonies per c c, become necessary, if the two phases are to be distinguished properly. This precaution, if taken

at all, was not stated by most of the preceding workers. In any case, assuming that the evidence for septicemia is unimpeachable, it must be remembered that 15 to 35 per cent of such patients recover in the absence of any but surgical and supportive treatment. Consequently, a single case or two does not carry sufficient weight for statistical purposes, and of the 27 references cited, only six^{18, 21, 24, 27, 30, 31} report more than five patients. In the absence of detailed information, therefore, both clinical and bacteriological, the reader, while accepting recovery as genuine, is unable to evaluate its significance.

It seems to the writers, however, that the crux of the matter resides in one all-important consideration. Experimental observations amply demonstrate that sulfonamide derivatives possess the capacity to suppress the growth of staphylococci, not only *in vitro* but *in vivo* as well. This suppression expresses itself, however, not as a bactericidal or bacteriostatic effect, but as a temporary retardation of growth. In time, growth which has been proceeding at a delayed rate, may then occur in the usual logarithmic manner. Consequently, it is not unlikely that in occasional patients (i.e., when the virulence of the infecting organism is not too highly exalted, when septicemia is in an early stage, when the number of staphylococci per c.c. is low, when the localized lesions are surgically accessible, when the general resistance of the patient is of good quality, etc.) the effect of drugs by restraining even for a period the otherwise rapid multiplication and invasion of the organism may actually give the tissues an opportunity to marshal their own defenses. In such instances the drugs may be helpful, but not curative, since in the ultimate analysis the patient must mobilize his own protective responses if the staphylococci are to be killed and eliminated, or if the infection is to terminate with recovery. In other words, this appears to be another example of the benefits reported in this connection during the past generation as a result of a number of different, non-specific agents, both chemical and biological, which have been advanced and later either gradually discarded or reserved for special, limited use. It seems to the writers, therefore, that while under certain conditions such as those enumerated, patients may recover because of the benefit conferred by the drugs, the more general rule may eventually be accepted that the sulfonamide derivatives are not strikingly effective in checking the majority of *genuine* staphylococcal septicemias.

SUMMARY AND CONCLUSIONS

1 A large number of patients (62) with staphylococcal septicemia, referred for possible serum therapy, had previously been under sulfonamide treatment.

2 Of these, 18 were given sulfanilamide, 12 sulfapyridine, 2 sulfamethylthiazole, 20 sulfathiazole, and 10 combinations of the different compounds.

3 In all these patients, the evidence suggests that the drugs failed to suppress the infection

4 Of the 62 patients, however, 20 eventually survived, presumably because of other treatment. If this number be disallowed as discussed above, the mortality rate is still 67 per cent or approximately the usual average in such infections

5 It is realized, however, that successfully treated patients were not referred to the writers, so that this report makes no pretense at statistical validity

6 Under special conditions, which are enumerated, it may be that the sulfonamides have a certain value in staphylococcal septicemia, but such examples are probably in the minority

7 In support of the above opinion is the *in vitro* observation that sodium sulfathiazole in concentrations as high as 30 per cent, which is effective in sterilizing completely heavy growths of *B. coli* in less than 15 minutes, has little if any restraining influence on different strains of *Staphylococcus*, even after one hour exposure

REFERENCES

- 1 HEUBNER, W. Chemotherapie von Infektionskrankheiten, Klin. Wchnschr., 1940, xix, 265, 289
- 2 KOLMER, J. A. Progress in chemotherapy of bacterial and other diseases, with special reference to prontosils, sulfanilamide, and sulfapyridine, Arch. Int. Med., 1940, lxxv, 671-743
- 3 REIMANN, H. A. Infectious diseases. A review of significant publications in 1939-1940, *ibid.*, 1940, lxxvi, 478-525
- 4 JULIANELLE, L. A. Observation on the specific treatment (Type A antiserum) of staphylococcal septicemia, ANN. INT. MED., 1939, xiii, 308-316
- 5 FORSTER. Sepsis in Anschluss an ausgedehnte Peripartitis. Heilung durch Streptozon, Zentralbl. Haut u. Geschlechtskr., 1933, xlv, 549. Cited by Kolmer²
- 6 MITCHELL, A. Treatment of acute osteomyelitis by Uleron, Brit. Med. Jr., 1938, ii, 1200-1
- 7 COLFROOK, L., and KENNY, M. Treatment of human puerperal infection and of experimental infection in mice with prontosil, Lancet, 1936, i, 1279-1286
- 8 MINDELL, T. H. Staphylococcal septicemia, Arch. Int. Med., 1939, lxxiii, 1068-1083
- 9 THORNTON, W. A., SWART, H. A., and REE, C. Sulfanilamide in staphylococcal septicemia, Jr. Am. Med. Assoc., 1939, cxiii, 1638-1639
- 10 BLAKE, F. G., and HAVILAND, J. W. Sulfapyridine in pneumococcal, streptococcal, and staphylococcal infections, Trans. Assoc. Am. Phys., 1939, liv, 130-148
- 11 FENTON, W. J., and HODGKISS, F. Staphylococcal septicemia treated with M and B 693, Lancet, 1938, ii, 667-668
- 12 GALFUSKI, S., and STANULIS, H. S. Septicemia due to *Staphylococcus albus* and treated with M and B 693, Lancet, 1939, ii, 1067-1068
- 13 GOLDFERG, S. I., and SACHS, A. Sulfapyridine in the treatment of *Staphylococcus aureus* bacteremia, Jr. Am. Med. Assoc., 1939, cxiii, 1639-1641
- 14 HARTMANN, A. F., BARNETT, H. L., PERLEY, A. M., and RUHOFF, M. B. Present status of therapy with sulfanilamide and sulfapyridine, Jr. Missouri State Med. Assoc., 1940, xxxvii, 41-54
- 15 LONG, P. N. Sulfapyridine, Jr. Am. Med. Assoc., 1939, cxii, 538-539
- 16 MARTIN, W. B., and BRYAN, R. Treatment of severe *Staphylococcus* infections with sulfapyridine or its sodium salt, South. Med. Jr., 1940, xxxiii, 1039-1044

- 17 O'BRIEN, E J, and MCCARTHY, C J Staphylococcal septicemia treated with M and B 693, *Lancet*, 1938, ii, 1232-1234
- 18 SPINK, W W, HANSEN, A E, and PAINE, J R Staphylococcic bacteremia Treatment with sulfapyridine and sulfathiazole, *Arch Int Med*, 1941, lxxvii, 25-35
- 19 WADE, H J Staphylococcal septicemia treated with M and B 693, *Lancet*, 1939, i, 756
- 20 CARROLL, G, KAPPEL, L, JONES, L, GALLAGHER, F W, and DiRocco, F W Sulfamethylthiazole A report of its clinical use in *Staphylococcus* septicemia with apparent success Report of animal experiments, *South Med Jr*, 1940, xxxiii, 83-87
- 21 HARTMANN, A F Personal communication
- 22 HERRELL, W E, and BROWN, A E The clinical use of sulfamethylthiazole in infections caused by *Staphylococcus aureus* Preliminary report, *Proc Staff Meet Mayo Clin*, 1939, xiv, 753-758
- 23 WEISMAN, D, and RUSSELL, H The treatment of acute staphylococcic infection with sulfamethylthiazole, *Jr Pediat*, 1940, xxvii, 31-37
- 24 CAREY, B W Use of sulfanilamide and related compounds in diseases of infancy and childhood, *Jr Am Med Assoc*, 1940, cxv, 924-929
- 25 FITCH, T S P Sulfathiazole in *Staphylococcus aureus* Epidermal abscess with septicemia and pyemia, *Arch Pediat*, 1940, lvii, 119-124
- 26 KELIHER, T F, and CARLAN, S A Treatment of staphylococcal septicemia with sulfamethylthiazole Report of a case with recovery, *Med Ann District of Columbia*, 1940, ix, 78-80
- 27 RANMELKAMP, C H, and KEEFER, C S Sulfathiazole therapy of *Staphylococcus aureus* bacteremia, *New Eng Jr Med*, 1940, ccxxiii, 877-885
- 28 SCOTT, G A Effect of sulfonamides on blood-serum, *Lancet*, 1939, ii, 244-246
- 29 STIRLING, W C Sulfathiazole Two cases of septicemia with recovery, *Jr Am Med Assoc*, 1940, cxv, 118-120
- 30 ABRAMSON, A W, and FLACKS, B Staphylococcal septicemia complicating carbuncle of face Recoveries after treatment with M and B 692, *Lancet*, 1939, ii, 1065-1067
- 31 HERRELL, W E, and BROWN, A E Treatment of septicemia, *Jr Am Med Assoc*, 1941, cxvi, 179-183
- 32 JULIANELLE, L A Determination of staphylococcal types by fermentation of mannite, *Proc Soc Exper Biol and Med*, 1937, xxxvi, 117-119
- 33 JULIANELLE, L A, and WIEGHARD, C W Immunological specificity of *Staphylococci*, *Jr Exper Med*, 1935, lxi, 23-30, also 31-37

THE VALUE OF STERNAL MARROW ASPIRATION AS A METHOD OF BONE MARROW BIOPSY *

By ERNEST H. FALCONER, M D , C M , F A C P , and MAURICE E
LEONARD, M D , C M , *San Francisco, California*

THE purpose of this paper is to attempt an evaluation of the method of aspirating portions of the sternal marrow through a needle or a small canula for study of the marrow cells. The assumption is that by this procedure a fair sample of the cellular components of the organ known as bone marrow can be obtained. Since Arinkin¹ first described this method in 1929, it has been widely used and has been the subject of a number of excellent papers. Some authors^{2, 3, 4, 5, 6} found the procedure satisfactory for study of the marrow. Others^{7, 8} apparently experienced difficulty in obtaining representative specimens of marrow and believed that aspiration specimens lack the fundamental architectural arrangement of the marrow without which the cellular relations can not be evaluated properly. They recommended instead the trephine operation. We do not attempt in this report to review the extensive literature concerning bone marrow biopsy, we merely record our experiences and comment on the specimens of aspirated sternal marrow studied, in an effort to evaluate the usefulness of this method of biopsy.

We employed the following technic. The skin over the upper sternum is painted with tincture of iodine and 2 per cent procaine hydrochloride is used as local anesthetic. A No. 16 lumbar puncture needle with a stylet, fashioned as shown in figure 1, is inserted into the outer table of the mid-sternum just below the junction of the manubrium and gladiolus. The ridge of this junction is easily identified, and with moderate pressure and a screwing motion the outer table can be perforated. A crunching sound indicates that the marrow cavity has been reached. The first suction pressure with a 5 c.c. Luer syringe frequently draws no marrow and it may be necessary to insert the stylet in order to remove a small plug of tissue or bone in the end of the needle. A few trials with gentle suction pressure may be necessary before the marrow is sufficiently liberated from the marrow spaces to appear in the syringe. About 0.2 to 0.3 c.c. of marrow is withdrawn. Spreads are made directly from the end of the needle. Drops of marrow are deposited on a cover glass, a second cover glass is placed over the drop so that the film spreads by capillary attraction. These films are stained with the Jenner-Giemsa stain.

With each set of cover glass films, a few prepared with 2 per cent cresyl blue were drawn in order to facilitate the study of reticulocytes in the mar-

* Received for publication May 2, 1941.

From the Department of Medicine, University of California Medical School, San Francisco.

Aided by a grant from the Christine Breon Fund for Medical Research.

row Differential counts were made on each specimen of marrow on the basis of 500 to 1000 cells counted Each author checked the count of the other and if essential differences occurred the average was selected Disagreement on the type of cell, which occurred occasionally, was settled by further study, consultation and reference to Osgood's atlas of the blood cells Our material comprised 180 marrow preparations which constitute the chief data of this paper Because of the simplicity of its classification, we used

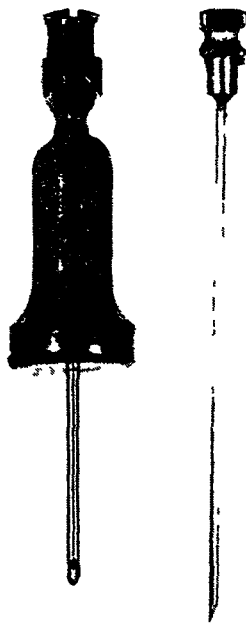


FIG 1

Arinkin's normal values (table 1) We believe, however, Segerdahl's figures for normal values (table 2) may be more reliable and accurate as they are based on cell counts of the marrow in 50 normal males from 20 to 30 years of age, 40 females in the same age group and 18 persons over 65 years of age We learned from Segerdahl personally that her "Reticulumzellen" are identical with our clasmotocytes, a cell type which we have added to Arinkin's table We have been much interested in the cell often referred to as—hematogone, a primitive cell resembling a lymphocyte but showing a very small rim of basophilic cytoplasm in which no granules are seen by ordinary staining The nucleus shows a densely matted chromatin We can not with confidence differentiate this cell from the lymphocyte

TABLE I
Normal Values According to Arinkin (Modified)

Cell Types	Per Cent
Myeloblasts	1 0 - 2 4
Promyelocytes	1 0 - 2 8
Myelocytes	
Neutrophilic	4 5 - 8 6
Eosinophilic	0 3 - 1 0
Metamyelocytes	1 4 - 3 4
Eosinophilic	0 3 - 1 0
Polymorphonuclears	
Neutrophilic	41 0 -55 0
Eosinophilic	0 6 - 4 0
Basophilic	0 0 - 1 0
Lymphocytes	7 3 -16 5
Plasma cells	0 3 - 0 9
Megakaryocytes	0 6 - 6 1
Monocytic cells	2 1 - 9 3
Pro-erythroblasts (including macroblasts)	0 8 - 2 9
Erythroblasts (including normoblasts)	5 7 -16 0
Clasmatocytes	0 03- 0 3

TABLE II
Normal Values According to Segerdahl *

Cell Types	Group 1 (50 men)		Group 2 (40 women)		Group 3 (18 old persons)	
	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation
Myeloblasts	1 32	0 57	1 20	0 53	1 23	0 70
Promyelocytes	1 35	0 76	1 65	0 58	1 62	1 01
Neutrophilic myelocytes	15 00	3 76	16 58	2 61	11 14	4 72
Eosinophilic myelocytes	1 37	0 63	1 45	0 83	1 17	1 20
Neutrophilic metamyelocytes	15 69	3 22	15 82	2 39	12 76	5 17
Neutrophilic stab/band forms	10 48	3 73	8 26	2 09	6 07	2 88
Neutrophilic polymorphonuclears	20 86	5 47	21 66	5 20	24 32	9 06
Eosinophilic polymorphonuclears	1 44	0 77	1 55	1 26	2 08	1 83
Basophilic polymorphonuclears	0 14	0 12	0 16	0 15	0 23	0 21
Monocytes	2.27	0 89	1 61	0 71	2 66	1 58
Lymphocytes	16 76	4 77	18 09	3 81	23 64	9 17
Erythroblastic series (all nucleated red cells)	12 88	4 39	11 50	3 22	12 37	6 20
Histiocytes ("Reticulumzellen")	0 03	0 07	0 05	0 08	0 09	0 11
Megakaryocytes	0 03	0 05	0 02	0 05	0 05	0 09
Plasma cells	0 39	0 35	0 42	0 23	0 55	0 56

* Adapted from Segerdahl, Table 4, p 66

Table 3 shows the results of studies on aspirated sternal marrow in 135 patients, with respect to diagnostic aid or confirmation of diagnosis gained through the procedure. The patients were grouped under the final clinical and laboratory diagnosis in each case. It is interesting to note that the diagnosis arrived at after thorough study of the case before sternal marrow aspiration was rarely changed by the data subsequently obtained through the study of the marrow cells. In 13 cases, aspirated sternal marrow and mar-

row preparations obtained by the trephine method were compared. In only one of these were significantly superior preparations as to number, type and distribution of cells obtained by the trephine method. This was a case of extensive arterial occlusion with thrombocytosis in which study of the number and distribution of megakaryocytes in the marrow was facilitated by the trephine preparations (figures 2 and 3). The marrow aspiration films

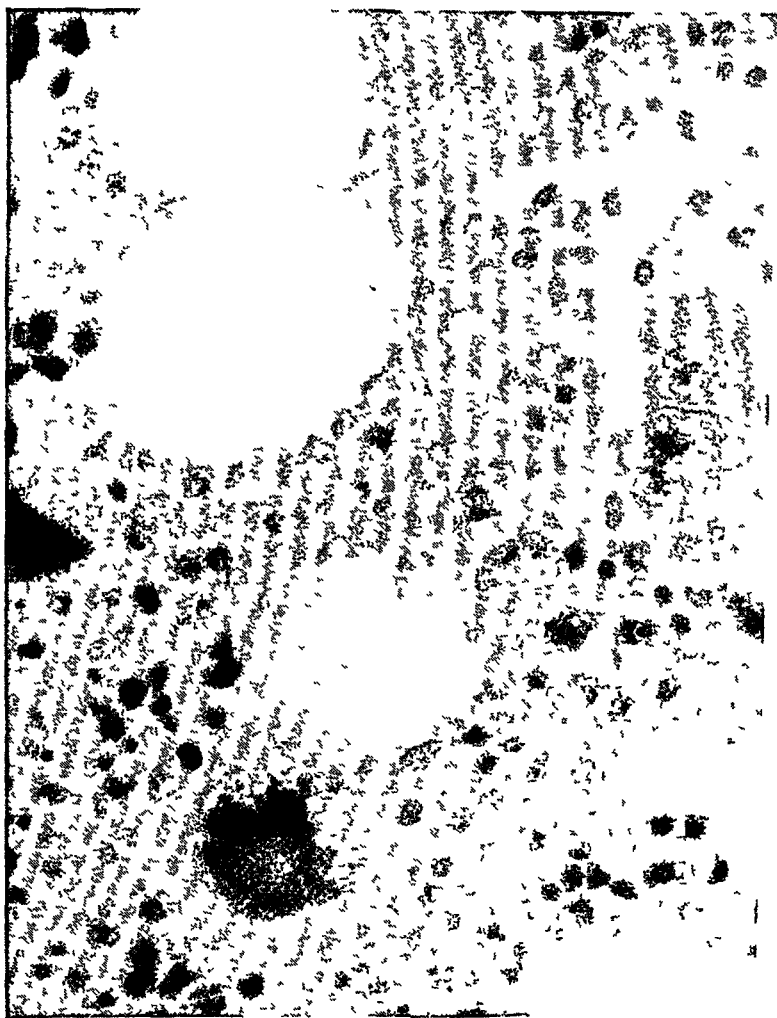


FIG 2 From patient with thrombocythemia. Increased number and distribution of megakaryocytes (Trephine biopsy)

showed striking instances of megakaryocytes surrounded by huge agminations of platelets (figure 3). This picture was not seen in the films of marrow obtained by the trephine method. We studied sections from fixed tissue preparations of marrow obtained by the trephine method in only three of the 12 cases. Custer and others^{7,8} have ascertained that study of such preparations is of great value. These preparations particularly show the changes in the architecture of the marrow and carry diagnostic implications

which would be missed in films of aspirated marrow One case from the Hodgkin's group, which is reviewed on page 455, illustrates this point

An analysis of table 3 according to groups shows that sternal marrow studies of the cases of subleukemic (aleukemic) and monocytic leukemia and of plasmacytoma gave definite information helpful in diagnosis and prognosis Lymphatic and myelogenous leukemia can usually be readily identified without differential marrow cell counts The captions, "aid to

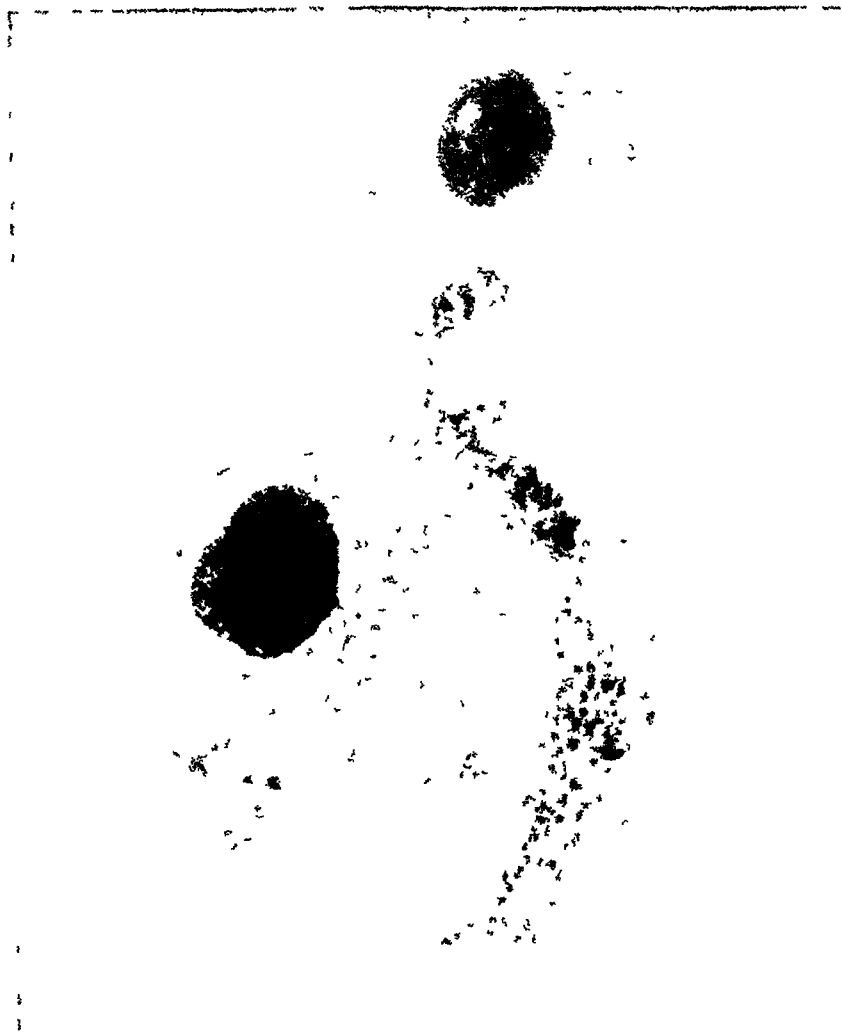


FIG. 3 Patient with thrombocythemia Megakaryocytes shown in aspirated marrow

diagnosis " and " confirmation of diagnosis " require clarification By " aid to diagnosis " we mean that the percentage or the myeloid-erythroid ratio of certain types of marrow cells, or both together, gave added information indicative of some definite lesion or recognized type of dysfunction of the hematopoietic system " Confirmation of diagnosis " indicates that marrow studies narrow the field of diagnostic possibilities by ruling out or ruling in suspected alterations in marrow function or morphology, thus they confirm the original diagnosis Such evidence may be purely negative

TABLE III
Grouping of Cases According to Diagnosis

Diagnosis	Number of Cases	Number of Marrow Specimens Studied	Abundant Cellular Material	Inadequate Cellular Material	Aid to Diagnosis	No Aid to Diagnosis	Confirmation of Diagnosis	Trephine and Aspiration Used	Diagnosis by Marrow Study
Leukemia									
Lymphatic	18	28	28		18		18		
Myelogenous	10	15	15		10		10		
Subleukemic acute	3	3	3		3		1		2
Monocytic	7	11	11		7		5		2
Multiple myeloma	7	9	9		6		6	1	1
Anemia									
Hypochromic	10	10	8	2	8	2	8		
Pernicious	10	13	13		10		10		1
Hyperchromic	4	6	6		4		4		1
Aplastic	8	14	14				3	3	1
of Carcinoma	3	3	3		3		3	1	1
Hemolytic anemia									
Icteric type, acquired	2	3	3		2		2		
Familial	1	2	2		1		1		
Purpura, thrombocytopenic	5	5	5		0	5	5	1	
Polycythemia vera	8	10	10		0	6	0	1	
Chronic leukopenia with neutropenia	5	5	5		0	5	0		
Chronic infections (2 cases of bacterial endocarditis)	7	7	7		1	6	2		1 (marrow culture)
Agranulocytosis	2	2	2		2		2		
Boeck's sarcoid	3	3	3		0	3	0	1	
Thrombocythemia associated with arterial disease	1	4	4		1		1	1	
Leukemoid reaction	3	3	3		3		3		
Lymphoma									
Hodgkin's	14	20	20		1	10	4	4	1
Lymphosarcoma	4	4	4		0	4	0		
Total	135	180	178	2	80	41	88	13	11

The anemias have not been thoroughly studied. However, in cases of hypochromic anemia very little information was obtained by sternal puncture. In the sternal marrow of pernicious anemia the presence of megaloblasts, especially in untreated patients, practically established the diagnosis. In one patient with a clinical and laboratory diagnosis of pernicious anemia, roentgenograms of the spine showed extensive demineralization and a compression fracture of the second lumbar vertebra. The sternal marrow was examined at intervals of four days after institution of parenteral liver therapy. An

initial sternal puncture had been secured before treatment was begun. The curve of maturation of the erythropoietic elements was used to test the response to therapy and it was paralleled exactly by the behavior of the cellular elements of the peripheral blood. In a patient with prostatic hypertrophy, urinary obstruction and infection, operation was postponed because of the accompanying anemia. Investigation showed a macrocytic hyperchromic anemia. No free hydrochloric acid appeared after histamine administration. The differential marrow cell count revealed a low myeloid-erythroid ratio with 11 per cent megaloblasts—an indication of pernicious anemia. The patient was placed on optimal doses of parenteral liver extract (Lederle, 1 cc = 15 units). After two weeks the reticulocytes had not risen significantly and during the last days of the trial treatment from 20 to 24 per cent of monocytes in mature and immature forms appeared in the marrow, a few also appeared in the peripheral blood. Roentgenograms of the skeleton showed no metastases or other lesions. The working diagnosis was changed to subleukemic monocytic leukemia or aplastic anemia.

In the hyperchromic anemias other than Addison's, the aspiration method was of value chiefly in differential diagnosis. In one patient with malnutrition and avitaminosis following prolonged diarrhea and vomiting, the sternal marrow so closely resembled that found in pernicious anemia that differentiation was possible only after failure of response to liver therapy and after spontaneous return of the marrow to a normal pattern when a proper state of nutrition had been restored. The eight cases of aplastic anemia presented distinctly cellular marrows. In each case the marrow presented certain individual variations not found in the others. They could be divided into the two groups described by Rhoads and Miller.⁹ Their Group 2, aplastic anemia with hyperplastic marrow, would include four of our cases, and their Group 3, aplastic anemia with active marrow, would include the remaining four. The marrows of our patients of the Group 2 type showed a high percentage of primitive cells and in this respect suggested subleukemic leukemia. The marrows of our patients of the Group 3 type more nearly resembled the marrow picture of pernicious anemia. In two of these patients aplastic anemia had developed following administration of the arsphenamines. Two of our patients with aplastic anemia had 6 to 10 per cent plasma cells in the marrow. One of these also had as high as 15 per cent monocytes in the peripheral blood but the marrow showed only 1 to 2 per cent of these cells. One patient, a young woman 22 years of age, had the typical findings of aplastic anemia in her peripheral blood with marked decrease of hemoglobin and of all the cellular elements of the blood. She had been kept alive for over a year by transfusions. Examination of her sternal marrow revealed an active marrow, especially in erythroid elements. Splenectomy was done whereupon the peripheral blood gradually returned to normal. For several months there was only slight change in the differential marrow cell count except that the megakaryocytes were increased and the

platelets markedly increased. This finding suggests that the spleen in some manner inhibited the delivery of cells to the peripheral circulation.

The few observations made in cases of hemolytic anemia showed no noteworthy changes in the marrow except for active erythropoiesis. The same may be said of the cases in the polycythemia vera and thrombocytopenic purpura groups. The latter showed very few platelets in the marrow. In one patient megakaryocytes were increased which in this instance proved to be a favorable prognostic sign. In the two patients with agranulocytosis the maturation of the marrow was arrested at the level of the early myeloid elements. There was nothing characteristic in the marrows of the group with chronic infections. One of the patients in this group, a woman 52 years of age, had the clinical characteristics of subacute bacterial endocarditis. She was weak, pale, had a swing of two to three degrees in daily temperature, had a rough presystolic murmur leading up to the first sound and a history of a former cardiac lesion. Her spleen was barely palpable on deep inspiration. Four blood cultures from venous blood taken during her hospitalization were negative. Sternal marrow aspiration was done and at the same time 10 c.c. of blood were withdrawn from the right median basilic vein. Both blood and marrow specimens were placed in brain broth media and incubated. The blood culture was negative, the marrow culture yielded an organism of the *Streptococcus viridans* type. Later in the course of the disease blood cultures yielded an organism of similar type. The marrow in Boeck's sarcoid yielded no contributory information as to diagnosis. In one patient in whom both the aspiration and the trephine methods of biopsy were used, the former showed a myeloid-erythroid ratio of 1:7.8 and the latter, 2:7.6. The specimen obtained by the trephine method yielded the lesser number of erythroblastic elements.

The lymphoma group, including Hodgkin's disease and lymphosarcoma, and the leukemoid group constituted an interesting study. Certain patients in these groups showed metastatic extension in one or more portions of the osseous system with evident marrow irritation. We have noted especially in Hodgkin's disease that a high white blood cell count (above 20,000 cells per cubic millimeter) with a myeloid reaction usually indicates skeletal involvement associated with either marrow metastases or irritation of the marrow. The sternal marrows in this group in some instances showed a leukemoid or myeloid reaction difficult to distinguish from the early myeloid reaction of myelogenous leukemia. A distinguishing point appears to be a lower myeloid-erythroid ratio than is found in leukemia (see table 4). The megakaryocytes were not increased in the marrows of the patients with Hodgkin's disease and lymphosarcoma, the percentage varied from 0.2 to 2 while in the majority of the patients with Hodgkin's disease it was 0.2 per cent. The marrow specimen of a patient with lymphosarcoma showed many megakaryocytes (figure 4) in a thick portion of the smear. This patient had

extensive metastatic involvement of the spine and 53,000 white blood cells—findings which indicate marrow as well as bone involvement

Table 4 gives a graphic representation of the myeloid-erythroid ratio of some of the groups discussed in connection with table 3 It has no importance aside from indicating a certain trend of the ratio in some of the

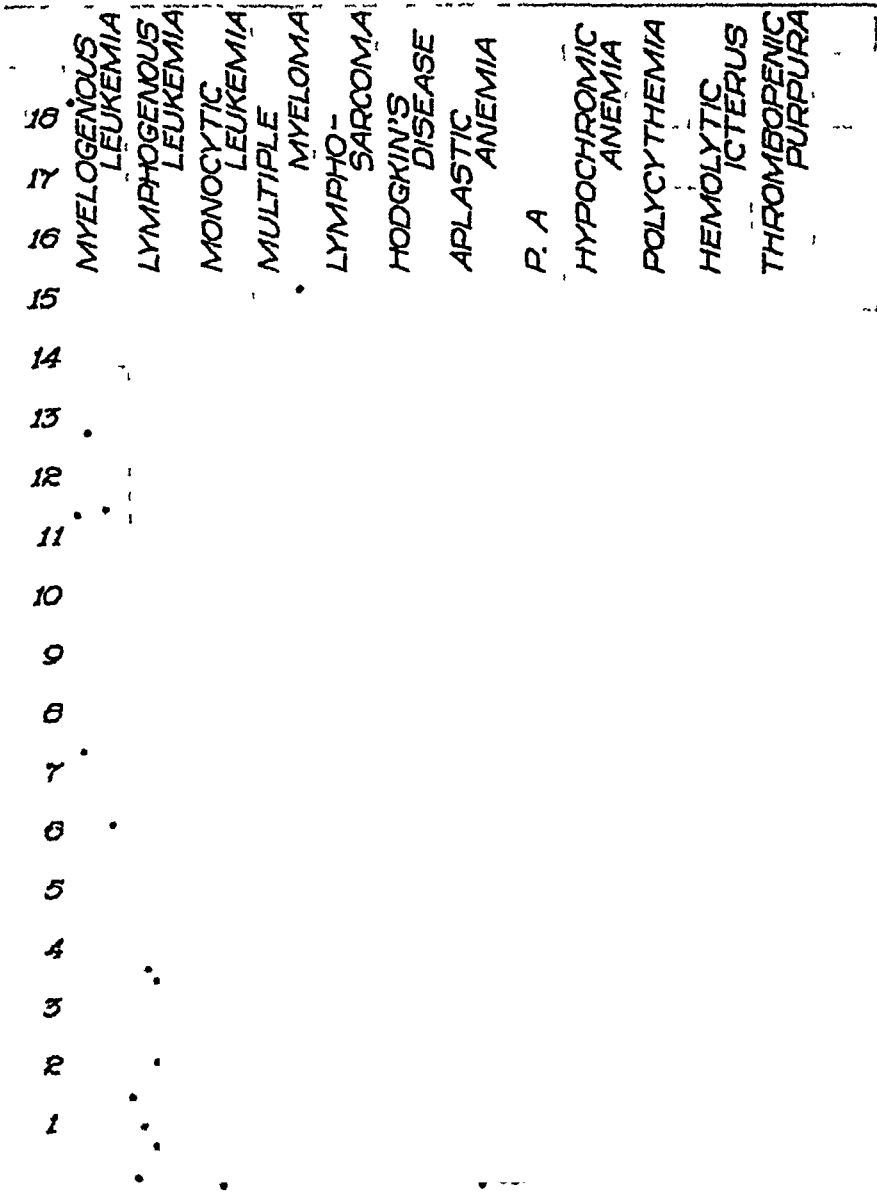


TABLE 4 Myeloid-Erythroid ratio—Each dot represents the figure obtained by dividing the myeloid by the erythroid elements

groups, while in other groups, such as the Hodgkin's group, the ratio shows a scatter

The case reports which follow illustrate the limitations as well as the usefulness of sternal marrow studies as an aid in diagnosis and prognosis of blood dyscrasias



FIG 4 Increased number of megakaryocytes in marrow of patient with lymphosarcoma

CASE REPORTS

Case 1 An Italian man, aged 54, complained of weakness, fever and "night sweats" On August 26, 1940, hemoglobin was 56 per cent, red blood cells 3,700,000, white blood cells 5,700 with lymphocytes 44 per cent and monocytes 14 per cent The liver and spleen were greatly enlarged Diagnosis of brucellosis was tentatively excluded by negative agglutination and phagocytic index tests According to the history the lymph nodes in the left cervical triangles had been somewhat enlarged but had been reduced to normal size after a few roentgen-ray treatments Differential diagnosis of Hodgkin's disease, Banti's disease or subleukemic leukemia was considered The sternal marrow obtained by aspiration showed a myeloid-erythroid ratio of 46.6:34.8 No maturation arrest of myeloid elements was apparent at an early level of maturity but a certain amount of fibrous tissue was noted in the films A trephine specimen of marrow showed, after fixation, an architectural arrangement of areas of active marrow with scattered areas of considerable fibrosis Later biopsy specimen of a lymph node revealed the histologic picture of Hodgkin's disease Splenic puncture did not contribute to diagnosis Roentgen treatment decreased the size of the liver and spleen but ascites appeared and the patient failed rapidly

Case 2 A woman 67 years of age had a "swelling in the right breast" in which the whole breast became involved Examination of the blood revealed a white cell count of 40,000 with an increased percentage of lymphocytes There were enlarged lymph nodes in the right axilla The hardness and nodular character of the mass in the breast suggested a carcinoma The question at issue was whether the blood picture could be explained on basis of the breast lesion The sternal marrow revealed 84 per cent lymphoblasts and 65.2 per cent lymphocytes Biopsy of an axillary node revealed carcinomatous metastases into a node which showed the histological pattern of lymphogenous leukemia

Case 3 A man, aged 57, had enlarged, matted nodes in the left anterior cervical triangle The spleen was palpable Red blood cells and hemoglobin were normal White blood cells numbered 7,200 of which 57 per cent were polymorphonuclear cells 23 per cent lymphocytes and 20 per cent monocytes Biopsy of one of the cervical lymph nodes was diagnosed "malignant lymphoma, stem cell type, probably monocytic leukemia" The sternal marrow showed a moderate myeloid hyperplasia with 8 per

cent lymphocytes and only 2 per cent monocytes. A diagnosis of Hodgkin's disease was made on the basis of the marrow findings. The subsequent course of the disease confirmed this diagnosis.

Case 4. In November 1937 a woman, aged 59, was studied because of failure to respond to parenteral liver extract, after a diagnosis of pernicious anemia had been made. She showed a smooth, glistening tongue, she had no free hydrochloric acid in the gastric contents after histamine, her cervical and axillary lymph nodes were palpable and her liver and spleen were enlarged. Red blood cells were 2,800,000, hemoglobin 58 per cent and white blood cells 5,700 with 52 per cent lymphocytes which later rose to 74 per cent of a total white blood count of 5,250 cells. Sternal marrow showed 20 per cent lymphocytes and a moderate increase of myeloid cells. A tentative diagnosis of early lymphatic leukemia was made. After following the patient for over three years during which time the hematologic findings remained about the same, the diagnosis was changed to Hodgkin's disease. We are awaiting the patient's permission to do a biopsy of a lymph node.

Case 5. This patient, a young Italian girl aged 17, was seen in consultation because of a severe reaction following a blood transfusion during which the temperature rose to 107° F. About three months previously she had been admitted to a hospital because of marked prostration, fever and anemia. Her white blood cell count had been 2000, with only about 20 per cent polymorphonuclear cells. A diagnosis of agranulocytosis had been made and two transfusions had been given with apparent benefit. Upon her return home the anemia and leukopenia persisted. When she was readmitted to the hospital the day before the severe transfusion reaction, her white blood cell count was 800 per cubic millimeter. One of the stained blood films made during hospitalization was reexamined and cells that had been classified as peculiar lymphocytes were recognized as monocytes. A bone marrow examination revealed 8 per cent monoblasts and 47.4 per cent monocytes. The patient died five days after the transfusion reaction. The obvious diagnosis was subleukemic monocytic leukemia.

Case 6. A woman aged 62, was seen in consultation because of an unexplained severe anemia associated with marked prostration and palpable lymph nodes in the submaxillary region. The results of previous thorough laboratory and clinical studies had been negative with the exception of the white blood cell count which ranged from 10,000 to 15,000 and showed from 20 to 42 per cent monocytes. Three sternal marrow aspirations taken at intervals showed monocytes up to 24 per cent and monoblasts up to 12 per cent. A diagnosis of monocytic leukemia was made.

Case 7. A man, aged 78 years, had been under treatment in a sanatorium for three months because of unexplained severe anemia. When he was seen at home (he had been dismissed from the sanatorium in a state thought to be terminal, with marked emaciation, prostration and delirium) his red blood cells were 1,900,000, hemoglobin 38 per cent, white blood cells 4,000 with 49 per cent polymorphonuclears, 49 per cent lymphocytes and 1 per cent each of eosinophiles and monocytes. Sternal aspiration was at that time not permitted by the family. The patient was admitted to the hospital because he had sustained a fracture of the left hip. At that time roentgenograms showed a pathologic fracture of the upper portion of the femur apparently due to a metastatic malignant lesion. The sternal marrow revealed 25 per cent proplasmacytes and 18 per cent plasmacytes. A diagnosis of plasmacytoma (multiple myeloma) was made and substantiated by findings at autopsy.

Case 8. A man aged 65, who came under observation in 1936, had all the criteria necessary for a diagnosis of pernicious anemia except that a small amount of free hydrochloric acid was found in the gastric secretions. His reticulocyte response to parenteral liver extract was not satisfactory but his red blood cells and hemoglobin rose nearly to normal levels during three months of this treatment. They then slowly fell as the white blood cells decreased from 2,800 to 1,500 with from 80 to 94 per cent lymphocytes. Aspirated marrow films showed marked hyperplasia of the marrow,

particularly of the erythropoietic elements In 1937 the patient returned to his home in Boston He was again hospitalized and a complete examination, including bone marrow biopsy, was made He showed no response to a long course of therapy with liver given parenterally and raw liver juice given by mouth Transfusions administered during 1938 and 1939 resulted in only temporary improvement The white blood cells fell to 900, marrow biopsy done on January 25, 1939, showed "hypoplasia" Diagnosis was aplastic anemia

Case 9 A man, aged 63, with marked anemia had a normal white blood cell count with 2 per cent each of myelocytes and metamyelocytes Extensive spotty osteoporosis of the rib cage and the pelvic bones was considered to be due to carcinomatous metastases Marrow aspirated from the sternum (figure 5) showed a few clusters of carcinomatous cells Fixed tissue smears from the marrow obtained by the trephine method showed definite metastatic carcinoma



FIG 5 Aspirated marrow showing cluster of carcinoma cells in patients with bone metastases

SUMMARY

In our experience sternal aspiration has been satisfactory as a method of marrow biopsy It is easy to perform and does not cause any particular discomfort to the patient We have seldom failed to get a fair sample of

the sternal marrow. Our technic has improved especially during the past year as a result of accumulated experience. The question of the diagnostic value of aspirated marrow specimens is largely one of individual opinion and experience. Obviously this method should not be used to supplant or short-cut other recognized diagnostic procedures, as our knowledge of the specific information gained from marrow studies is as yet rather limited. Sternal marrow aspiration should be employed as a means of gaining information regarding the morphology of the marrow cells as well as their respective number in diseases involving the hemopoietic system. Such information should always be interpreted in the light of all other data at our disposal. When used in this manner with recognition of its limitations, the method has proved in our experience a distinct help. The trephine method should be used whenever the aspiration method appears inadequate.

An interesting field for further investigation is the study of the marrow in certain chronic infections, such as brucellosis and bacterial endocarditis. The method of marrow aspiration is particularly applicable to investigative studies of this type. We are using marrow cell counts as one means of checking results of therapy in several patients and hope to report useful data after sufficient observations have been made.

REFERENCES

1. ARINKIN, M. L. Die intravitale Untersuchungsmethodik des Knochenmarks, *Folia Haemat*, 1929, xxxviii, 159.
2. SIEGFRID, E. Ueber Sternalpunktionen, *Acta med Scand*, 1935, Suppl. LXIV.
3. YOUNG, R. H., and OSGOOD, E. E. Sternal marrow aspirated during life, *Arch Int Med*, 1935, lv, 186.
4. VOGEL, P., ERF, L. A., and ROSENTHAL, N. Hematological observations on bone marrow obtained by sternal puncture, *Am Jr Clin Path*, 1937, vii, 436.
5. REICH, C. A study of the diagnostic value of sternal puncture in clinical hematology, *Am Jr Med Sci*, 1935, clxxxix, 515.
6. HOLMES, W. F., and BROWN, G. O. Clinical study of bone marrow by the method of sternal puncture, *Proc Soc Exper Biol and Med*, 1933, xxx, 1306.
7. CLUSTER, R. P. Studies on the structure and function of bone marrow. III. Bone marrow biopsy, *Am Jr Med Sci*, 1933, clxxxv, 617.
8. DAMPSTRA, W., HENSTEN, H. H., and VALENTINE, E. H. The comparative value and the limitations of the trephine and puncture methods for biopsy of the sternal bone marrow, *Ann Int Med*, 1937, vi, 801.
9. RHOADS, C. P., and MILLER, D. K. Histology of the bone marrow in aplastic anemia, *Arch Path*, 1938, xxi, 648.

CHANGES IN THE CARDIAC SHADOW FOLLOWING PHARMACOLOGICAL "SHOCK" THERAPY OF SCHIZOPHRENIA *

By HAROLD W STERLING, M D , *Little Rock, Arkansas*, and CRAWFORD N BAGANZ, M D , *Lyons, New Jersey*

STUDIES of the heart following pharmacological shock therapy have been the object of many research projects. Fariell and Vassaf¹ reported changes in seven-foot teleoroentgenograms of the heart before, during, and after the insulin treatment of schizophrenia. In five of the six cases treated "there occurred a measurable enlargement of the cardiac shadow." These authorities also reported that "measurements of the heart were made at various intervals after the cessation of treatment, these showed reduction in the heart shadow to a size approaching that prior to treatment and coincidentally it was observed that the favorable therapeutic effects at the end of treatment failed to be maintained." They further suggested "that some of the mental improvement and cardiovascular changes associated with insulin shock therapy may be explained by stimulation of the sympathetic nervous system. It appears that when the therapeutic stimulation of the sympathetic system ceased, its favorable effects on the mental condition and on the cardiovascular system of the patient gradually subsided."

That insulin is of value in the treatment of malnutrition and that the utilization of insulin in large doses in "shock" therapy causes a marked gain in weight, are such commonplace observations as to verge upon triteness. Elementary physiological knowledge coupled with the daily experience of roentgenologists clearly demonstrates that with an increase of the intra-abdominal contents there is a concomitant rise of the diaphragm. This knowledge and experience further demonstrate that the rise of the diaphragm is accompanied by a marked change of the cardiac shadow, apparently due to rotation of the heart about a vertical axis. That there is a close relation between the height of the diaphragm and the size of the cardiac shadow is not new or original as the work of Chandlee and Burvill-Holmes² will certify. However, this fact has been commonly overlooked and frequently the only practical guide employed in estimation of the cardiac size has been the cardiothoracic ratio.

Field, in his studies of vitamin B₁, as displayed by the Upjohn Laboratories in their advertisements of the same,³ showed reproductions of teleoroentgenograms with marked changes in the contour of the heart shadow and an accompanying change in the height of the diaphragm. The changes

* Received for publication February 11, 1941

Published with permission of the medical director, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the author

in the height of the diaphragm are not mentioned as contributing factors to the change in the cardiac shadow

Messinger⁴ in his study of the effects of insulin shock therapy on the heart, excluded from his studies those cases in which teleoroentgenograms revealed an appreciable difference in the height of the diaphragm. As the authors believe that this factor is most important in determining cardiac contour, this paper concerns itself principally with an attempt to correlate this factor with differences in total diameter of the cardiac shadow.

Nineteen patients who had received insulin "shock" therapy for schizophrenia were studied for changes in cardiac outline (Table 1 and figure 1.)

TABLE I

Correlation of Changes in Cardiac Shadow with Changes in Height of Diaphragm in Cases That Received Pharmacological "Shock" Therapy

	Before Treatment		After Treatment	
	Height of Diaphragm*	Total Trans Diam Heart (cm)	Height of Diaphragm*	Total Trans Diam Heart (cm)
Case 1	21.8 cm	12.3 cm	20.4 cm	13.0 cm
Case 2	21.5 cm	13.0 cm	19.9 cm	15.4 cm
Case 3	30.2 cm	10.9 cm	27.5 cm	12.0 cm
Case 4	25.2 cm	11.5 cm	22.7 cm	12.4 cm
Case 5	24.0 cm	13.8 cm	22.3 cm	14.6 cm
Case 6	26.4 cm	11.6 cm	23.5 cm	12.8 cm
Case 7	24.3 cm	13.4 cm	24.0 cm	13.8 cm
Case 8	24.0 cm	12.5 cm	24.0 cm	12.7 cm
Case 9	25.1 cm	11.7 cm	20.2 cm	14.6 cm
Case 10	27.2 cm	12.0 cm	25.3 cm	13.3 cm
Case 11	25.0 cm	10.6 cm	23.5 cm	11.7 cm
Case 12	25.8 cm	11.4 cm	24.4 cm	14.5 cm
Case 13	20.6 cm	12.0 cm	21.0 cm	12.3 cm
Case 14	28.3 cm	12.0 cm	23.0 cm	15.0 cm
Case 15	25.8 cm	12.2 cm	25.5 cm	12.3 cm
Case 16	26.8 cm	10.4 cm	21.6 cm	15.0 cm
Case 17	27.5 cm	11.2 cm	26.0 cm	13.1 cm
Case 18	26.5 cm	11.2 cm	26.5 cm	11.2 cm
Case 19	22.0 cm	14.0 cm	20.2 cm	14.0 cm

* Height of diaphragm is expressed in centimeters from spinous process of first dorsal vertebra to dome of diaphragm, during deep inspiration.

These patients had one or more six-foot teleoroentgenograms of the heart prior to insulin therapy and one or more following the treatment. In addition to these 19 patients, there were three others who received insulin in sub-shock doses for treatment of malnutrition and who underwent marked gains in weight but who did not experience hypoglycemic coma. These three patients served as valuable controls and clearly demonstrated that changes in cardiac contour could take place without organic heart disease being present.

All patients were free from cardiac disorders prior to and following therapy.

The accompanying chart (table 2 and figure 2) shows the diaphragmatic changes, and changes in total diameter of the cardiac shadow at dif-

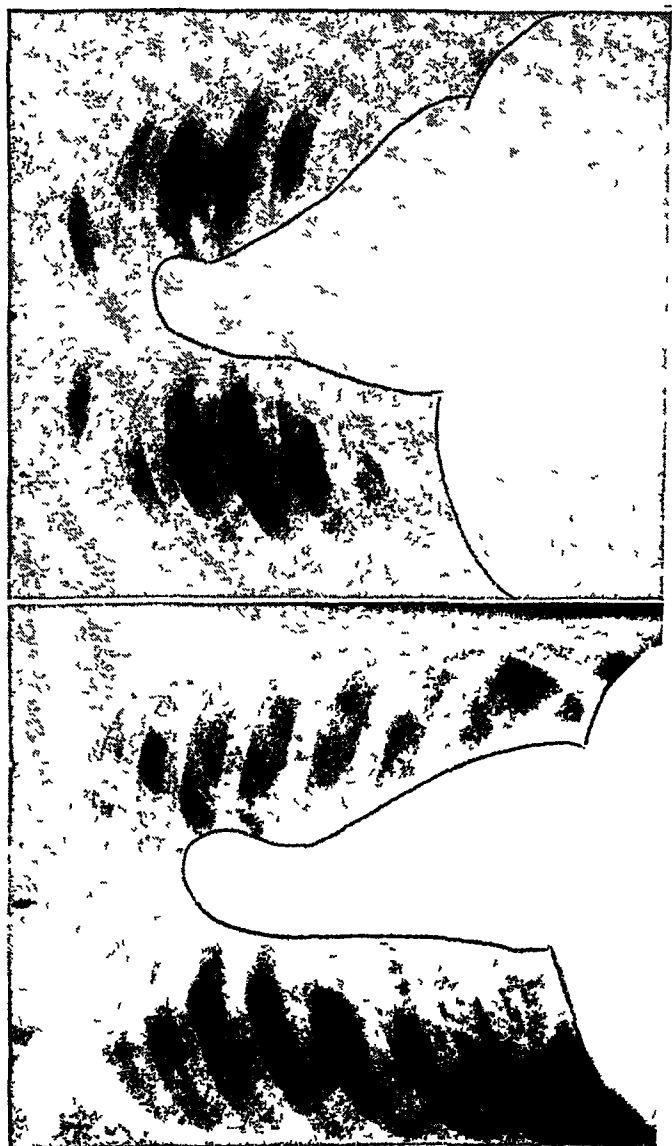


FIG 1 Reproduction of teleroentgenograms of case 16 (a) before insulin therapy, (b) after insulin therapy, (c) "a" superimposed upon "b" with spinous process of first dorsal vertebra at same level Diaphragm, cardiac outline and spinous process of first dorsal vertebrae have been retouched for greater contrast

TABLE II

Correlation of Changes in Cardiac Shadow with Changes in Height of Diaphragm in Cases That Received Sub-Shock Doses of Insulin for Treatment of Malnutrition

	Before Treatment		After Treatment	
	Height of Diaphragm*	Total Trans Diam Heart (cm)	Height of Diaphragm*	Total Trans Diam Heart (cm)
Case 20	26.5 cm	10.8 cm	21.0 cm	12.4 cm
Case 21	24.0 cm	11.1 cm	21.0 cm	13.8 cm
Case 22	26.0 cm	10.6 cm	25.0 cm	11.3 cm

* Height of diaphragm is expressed in centimeters from spinous process of first dorsal vertebra to dome of diaphragm, during deep inspiration

ferent stages of nutrition. Inasmuch as some authorities feel the cardiac changes described may have been of organic heart disease resulting from "shock" therapy, it is interesting to note that the three cases treated for malnutrition had the same changes in diaphragm and cardiac contours as the cases that underwent hypoglycemic coma. It is also worthy of notice that when one of these individuals who had been treated for malnutrition was removed from adequate dietary supervision and removed from sub-shock doses of insulin, he underwent a loss of weight almost to his previous level. Accompanying this relapse to his former weight was a return to a practically identical cardiac shadow and a lowering of the diaphragm to the former level.

Farrell and Vassaf noted a return of the previous cardiac shadow when insulin treated patients underwent a psychiatric relapse. The authors concur with the opinion of other workers in the field of pharmacological "shock" therapy that one of the first signs of an impending relapse is a marked loss of weight. Therefore, we believe that the weight loss of these relapsed patients and the change in cardiac contour have the relation of cause and effect, and further that this change is symptomatic of a relapse rather than serving as an etiological factor as suggested by Farrell and Vassaf.

SUMMARY

The authors have observed in the course of pharmacological "shock" therapy a change in the cardiac contour. It was first found that this change was an increase in total transverse diameter of the heart and that this increase roughly paralleled a gain in weight.

Further studies revealed a close correlation between the change in the height of the diaphragm and a change in the total transverse diameter of the heart.

The authors report three cases in which insulin in sub-shock doses was given for malnutrition and in which very similar changes were noted to those taking place in the cases receiving large "shock" doses of insulin.

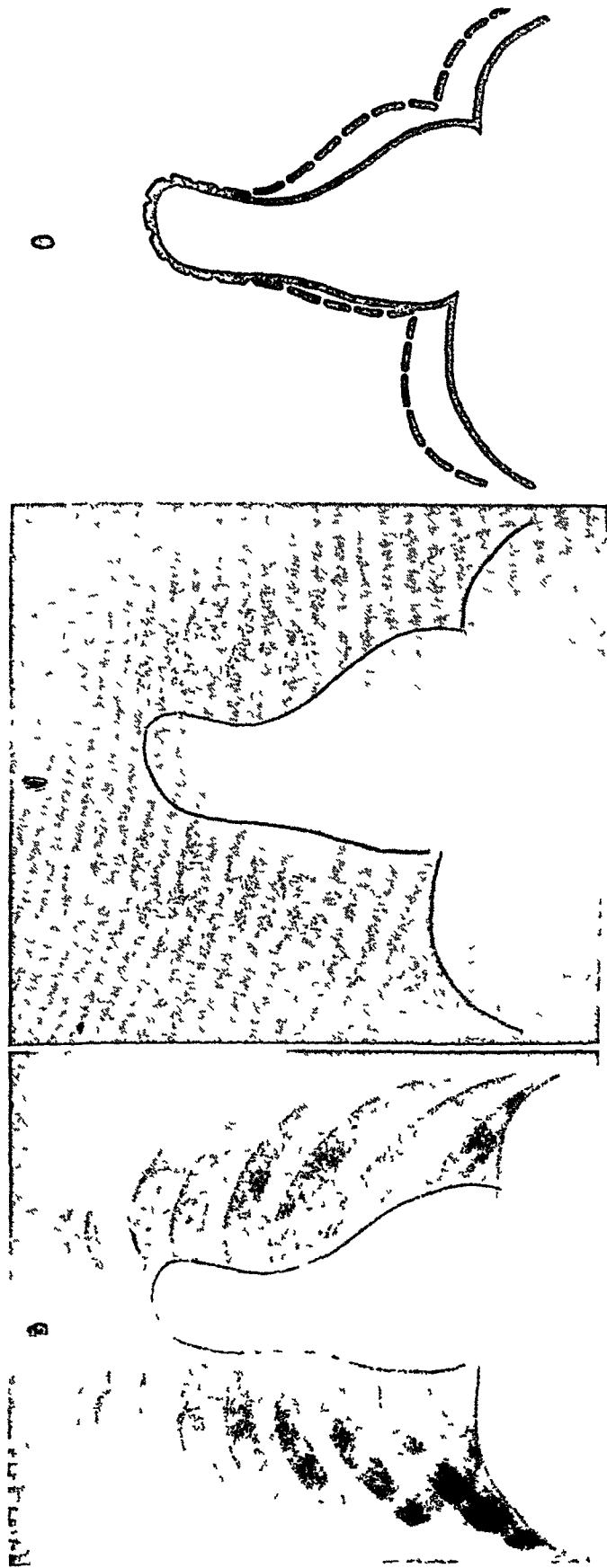


FIG 2 Reproduction of teleroentgenograms of case 20 (a) before insulin therapy, (b) after insulin therapy, (c) "a" superimposed upon "b" with spinous process of first dorsal vertebra at same level Diaphragm, cardiac outline and spinous process of first dorsal vertebrae have been retouched for greater contrast

CONCLUSION

It is the opinion of the authors that insufficient importance has been attached to the height of the diaphragm as one of the factors influencing the total transverse diameter of the heart as seen on a teleroentgenogram

BIBLIOGRAPHY

- 1 FARRELL, M J, and VASSAF, ETEM Effect of insulin shock on the heart and blood pressure in the treatment of schizophrenia, Arch Neurol and Psychiat, 1940, xliii, 784
- 2 CHANDLEE, G J, and BURVILL-HOLMES, E Clinical and roentgen-ray findings in the study of the heart, and great vessels, Am Jr Med Sci, 1929, clxxviii, 364
- 3 FIELD, HENRY, JR Advertisement in Jr Am Med Assoc, 1940, cxiv, 16
- 4 MESSINGER, EMANUEL Cardiovascular changes associated with the insulin shock treatment, ANN INT MED, 1938, xii, 862

ELECTROCARDIOGRAPHIC CHANGES IN STAB AND GUNSHOT WOUNDS OF THE HEART, WITH REVIEW OF THE LITERATURE*

By J SOLOVAY, M D , G D RICE, M D , *Veterans Administration Facility,
Camp Custer, Michigan*, and H U SOLOVAY, M D ,
Brooklyn, New York

SINCE the dawn of the twentieth century, many hundreds of stab and gunshot wounds of the heart in human beings have been treated surgically, but not until 1924 was a case with serial electrocardiographic tracings recorded¹ Heart wounds are still sufficiently novel that individual or multiple case reports continue to be published, but few of these contain complete electrocardiographic studies It would seem that such studies might offer a method of determining electrocardiographic changes produced by localized injury to different portions of the human heart

A patient with a stab wound of the left ventricle, who had repeated tracings made, has been observed at this hospital The changes noted were suggestive of pericarditis, and no evidence of a localized lesion of the myocardium could be found Koucky and Milles² collected nine cases of stab wounds of the ventricles and added one of their own They concluded "that the electrocardiographic changes noted are, as is the generally accepted opinion, purely myocardial in origin and are dependent on the degenerative changes that occur in the muscle fibers involved" On the other hand VanderVeer and Norris,³ who reviewed several recorded stab wounds of the heart, and added a case with traumatic laceration of the right auricle, stated "The progressive electrocardiographic changes in many cases of stab wound of the ventricle suggest acute pericarditis rather than a single anterior lesion of the myocardium" Our interest was stimulated by this divergence of opinion to review the cases with tracings that had been published Those which had abnormalities due to injury of some specialized tissue, such as the bundle of His, were not considered

That an inflammatory reaction of the pericardium is an almost universal complication of penetrating injuries of the heart has been recognized for many years Hesse,⁴ on the basis of a review of the after-results of 12 cases of his own and 107 cases from the literature, stated that the appearance of a dry pericarditis after heart suture could almost be considered a rule If not reported, it was probably due to failure on the part of the surgeon to observe it Beck⁵ mentions the high incidence of a postoperative pericardial effusion and subsequent pericardial adhesions The likelihood of these complications is apparent when it is considered that the traumatizing agent intro-

* Received for publication March 16, 1940

Published with permission of the Medical Director, Veterans Administration, who assumes no responsibility for the opinions expressed

duced is contaminated with bacteria, that there is free blood present in the pericardial sac, generally undue haste in the emergency operation, and that there is considerable manipulation of the heart incident to the operative intervention. In dogs Barnes and Mann⁶ have shown that mere opening of the pericardium resulted in extensive pericarditis. This was confirmed by Fowler, Rathe and Smith.⁷

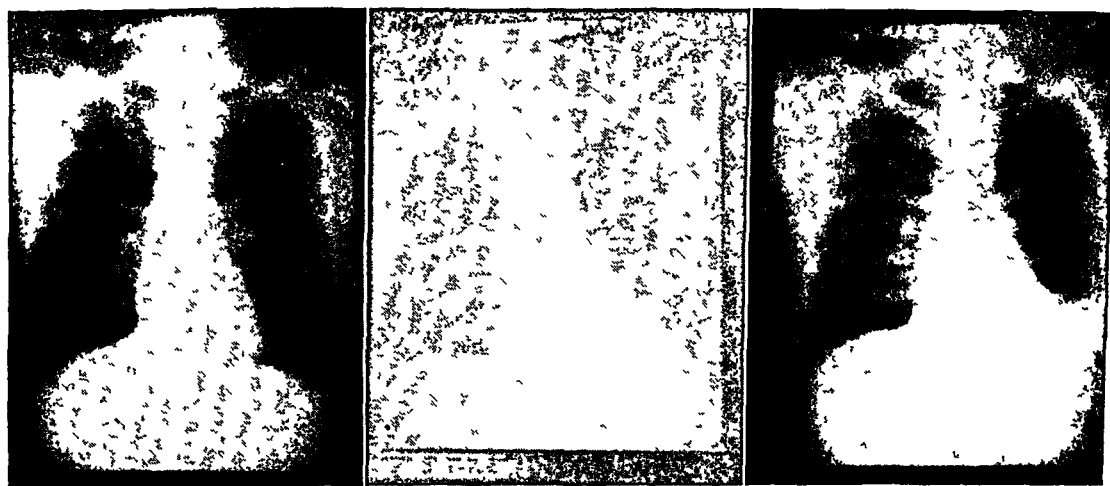
The importance also of the wound in the substance of the heart cannot be overlooked. There is an actual severance and necrosis of a localized portion of myocardium. In addition, the surrounding muscle is enveloped in suture material with resultant compression, trauma and ischemia of this larger area. Hesse,¹ in his article, cites two cases which died of pneumonia 6 and 18 days respectively after heart suture, in which autopsy showed the muscle about the wound to be necrotic, and two other cases in which aneurysm developed at the site of the operative scar. These are rare sequelae, but can be considered as indirect evidence of the destructive process which may occur in the sutured wound. In addition there is frequent ligation of a branch of the coronary vessels, usually the descending branch of the left coronary artery, either because it is damaged in the initial injury to the heart or because it is too close to the margin of the wound and has to be blocked by the sutures in order to close the hiatus in the myocardium. As a consequence of the closure of a coronary vessel, an infarct is probably always produced, in spite of the collateral circulation. Two cases of operative ligation of a coronary artery in human beings with postmortem demonstration of definite cardiac infarction have been found in the literature.^{8,9}

The electrocardiographic changes produced by pericarditis¹⁰ consist of an early and transient elevation of the RT segment in the first two leads or in all three leads. This elevation is generally most marked in Lead II and has, therefore, aptly been called the T_1 type by Paul Wood.¹¹ The deviation is in the same direction (upward) in all leads, unlike myocardial infarction where it is opposite in direction in Leads I and III. Also no significant Q pattern is developed. The electrocardiographic picture of acute myocardial injury, on the other hand, depends upon the location of the lesion. Thus a lesion of the anterior left ventricular wall produces the characteristic T_1 type, with early upward deviation of the RT segment in Leads I and II and downward displacement of this segment in Lead III, followed by inversion of T_1 and T_2 , whereas T_3 remains upright. No pattern due to anterior right ventricular injury in the human being has been definitely established, because infarction in this region almost never occurs.¹²

In our case report which follows and in the cases accumulated from the literature an attempt has been made to evaluate the electrocardiographic tracings in terms of all the factors operative in influencing them—the post-operative acute inflammatory pericardial reaction, the localized injury to the myocardium generally in the anterior wall of either the right or left ventricle, and the cardiac infarction if a coronary vessel was ligated.

CASE REPORT

The patient, C B., was a 44 year old white male, who had had dementia praecox for five years and who had received a course of insulin shock therapy during the summer of 1938, with a great deal of improvement in his mental condition. At 9 15 a m., September 3, 1939, he made a suicidal attempt by placing the point of a pencil of the eversharp type in the fifth intercostal space about 2 cm medial to the nipple line, and throwing himself on his face, embedding the pencil in the chest wall. When seen by a physician shortly after, he presented the classical, much-described picture of cardiac tamponade, venous engorgement and cerebral anemia. At operation left hemothorax was found, and a small transversely directed wound, about 4 to 5 mm in diameter was observed on the obtuse margin of the base of the left ventricle, from which a thin stream of blood spurted with each systole of the heart. The wound was readily closed by a superficially placed purse-string suture. The postoperative course was uneventful, except for a moderate pericardial and slight left pleural effusion (figure 1). The air in the left side of the thorax was absorbed very rapidly. Electro-



6 ft plate, 1 mo before operation

Bed-side plate 4 days post-operatively, showing pericardial effusion

Bed-side plate 20 days post-operatively, showing absorption of pericardial effusion, and presence of slight pleural effusion

FIG 1 Serial roentgenograms in Patient C B

cardiograms (figure 2) showed slight upward deviation of the RT segments in all leads, most marked in Lead II. These changes were apparent on the third postoperative day when the first tracing was taken and gradually diminished in extent until the tenth postoperative day, when the RT segments were again isoelectric except for the one in Lead II, which has continued to retain a barely perceptible elevation above the base line. At no time did the T-waves in any leads become inverted. Thus the electrocardiographic picture was that of the typical T_2 variety, presenting early transient changes most likely due to pericarditis. Other changes consisted of diminution in amplitude of the QRS complex in Leads II and III and flattening of the T-wave in Lead III.

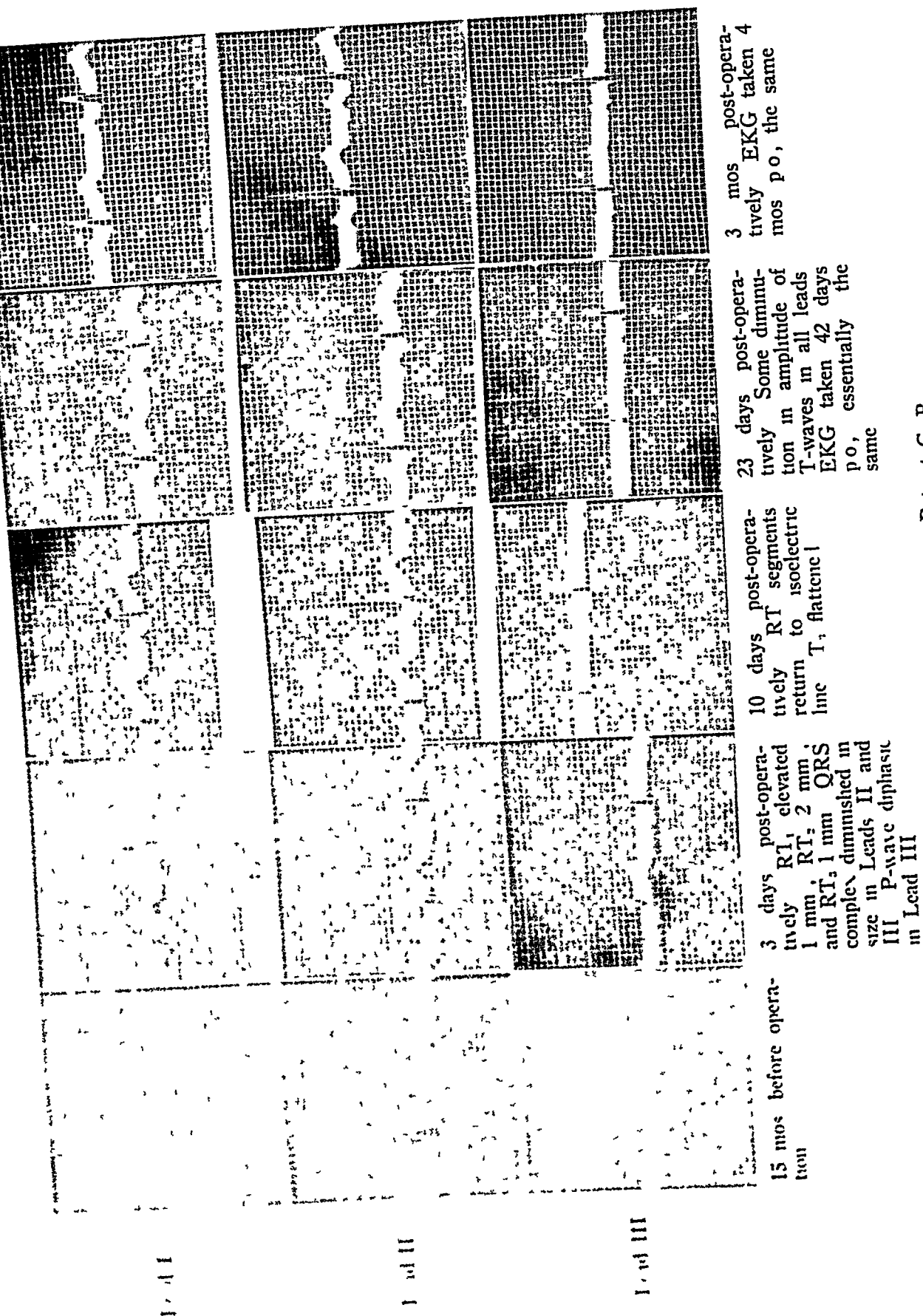


Fig 2 Serial electrocardiograms in Patient C B

RESULTS

The following table (table 1) contains a summary of the pertinent electrocardiographic findings in the 22 previously published cases, which are all that could be found in the medical literature available to us, and the present case report. Six of these had no early electrocardiograms, and three of the remainder had no late electrocardiograms because the patients died. A brief statement of the pathological findings of the heart in four patients is also made.

DISCUSSION

In 15 of the 17 cases listed in the above chart, in which tracings during the first week were taken, a T_2 type of curve appeared. The RT segments were elevated in the first two leads or in all leads, and generally most markedly in Lead II. In case 18 this was rapidly followed by T-wave inversion in all leads as early as the third day, which by the sixth day was showing signs of becoming upright again. In some of the patients, such as numbers 11, 12 and 14, the RT elevation in Lead III was very slight and was followed by transient T-wave inversion in that lead, which had usually disappeared by the end of the first week. These curves occurred early and were transient, as occurs typically in pericarditis.

The tracings made from two weeks to one month after suture of the heart wound were characterized generally by bow-shaped RT segments starting from the isoelectric line and by inverted T-waves. These reverted to normal in from two to six months in most cases. In wounds of the anterior surface of the left ventricle, with or without involvement of branches of coronary arteries serving this region, a late T_1 type of curve with inversion of T-waves in Lead I or Leads I and II was found. In those patients with injury to the right anterior ventricular wall, without damage to coronary vessels supplying the left ventricle, T-wave inversion in all three leads was present. Case 19 of this group was complicated by purulent pericarditis, which may have produced sufficient inflammatory destruction of the superficial layers of the myocardium to cause the T-wave changes. The latter changes in that case would have no bearing on the location of the wound. The remainder of this group of cases, although small in number, suggests that an injury of the anterior wall of the right ventricle may in its later stages produce T-wave inversion in all leads. This does not mean that lesions in other localities or combined lesions may not produce a similar electrocardiographic picture. Crawford et al.,²⁸ in contrast to the above, have demonstrated that cauterization of the base of the anterior surface of the right ventricle in cats produced no electrocardiographic changes. According to the muscle bundle method of electrocardiographic localization of Robb and Robb,²⁹ however, an injury of the superficial sinospiral muscle, part of which composes the outer layer of the wall of the anterior surface of the right ventricle, produces elevation of the RT segments in all leads and subsequent in-

TABLE I

Case No.	Age	Sex	Date of Death	Cause of Death	PO	Initial RT (changes)		Subsequent RT Changes		T-Wave Inversion		T-Wave Return to Normal		Q-Wave Changes if Any	Comments
						Time	Nature	Time	Nature	Time	Nature	Time	Final Picture		
1	28	Male	1956	Myocardial infarction	Yes					1 EKG 9 mos P O	T ₁ -2 mm T ₂ and T ₃ upright	1 EKG 1 yr P O	T ₁ diphasic +5-1 mm T ₂ and T ₃ upright	Significant Q ₁ in first tracing, became small in second	Late T ₁ type
2	35	Male	1956	Myocardial infarction	Yes			1st EKG 5 days P O	RT ₁ +5 mm RT ₂ +1 RT ₃ iso-electric (T ₃ inverted)	20 days P O 26 days P O	T ₁ and T ₂ inverted T ₃ upright T inverted in all leads	3 and 8 mos P O	T ₁ and T ₂ upright T ₃ inverted	Small Q ₂ and Q ₃ seen in 12-lead tracing and from then on	Early T ₁ type, late T ₁ type T ₃ however was inverted in all tracings except for transient period during acute inversion of T ₁ and T ₂ when it was upright
3	45	Male	1956	Myocardial infarction	Yes			1st EKG 3 wks P O	T inverted in all leads	1st EKG 3 wks P O	T inverted in all leads	6 mos P O	T ₁ upright T ₂ diphasic T ₃ inverted	Small Q ₃ develops after 7 weeks	Late T ₁ type T ₁ persistently inverted, after T ₁ and T ₂ have become upright
4	45	Male	1956	Myocardial infarction	Yes			1 EKG 37 days P O	T ₁ inverted T ₂ diphasic T ₃ upright	1 EKG 37 days P O	T ₁ inverted T ₂ diphasic T ₃ upright		Small Q ₁		Late T ₁ type (Taken from P Wood's)
5	45	Male	1956	Myocardial infarction	Yes			34 hrs P O	RT ₁ and RT ₂ as before RT ₃ iso-electric	RT ₁ and RT ₂ as before RT ₃ iso-electric	RT ₁ and RT ₂ as before RT ₃ iso-electric	3 mos P O	T-waves same as previous		Initial T ₁ type, subsequent T ₂ type Died 42 hours P O Autopsy showed fibrous pericarditis
6	45	Male	1956	Myocardial infarction	Yes			3 days P O	RT ₁ +1 mm RT ₂ +2 RT ₃ +1	RT ₁ +1 mm RT ₂ +2 RT ₃ +1	RT ₁ and T ₂ upright T ₃ flattened		None		Early T ₂ type No late signs of myocardial injury
7	45	Male	1956	Myocardial infarction	Yes			1 EKG 15 hrs P O	RT ₁ +1 mm RT ₂ +2 RT ₃ iso-electric	RT ₁ +1 mm RT ₂ +2 RT ₃ iso-electric	RT ₁ +1 mm RT ₂ +2 RT ₃ iso-electric				Died 36 hours P O Autopsy showed fibrino-purulent pericarditis

TABLE I (Continued)

Case No	Author, Year	Age, Color	Characteristics of Heart Wound	P O pericarditis	Initial RT Changes		Subsequent RT Changes		T-Wave Inversion		T-Wave Return to Normal		Q-Wave Changes If Any	Comments
					Time	Nature	Time	Nature	Time	Nature	Time	Final Picture		
8	Porter and Biggers 1932—Case 1	23 negro	A L V, on left border and parallel to long axis and 5 cm from apex. Meas 1 cm externally. Desc branch lift circumflex cor ligated	Yes	14 hrs P O	RT ₁ +2 mm RT ₂ +2 mm RT ₃ -1.5	4 and 5 days P O	RT ₁ +2 mm RT ₂ +1.5 RT ₃ +5 (T ₃ flat)	34 days P O	T ₁ and T ₂ inverted T ₃ upright	63 days P O	Upright in all leads	Small Q present in all leads in Lead III early growing smaller with time	Initial T ₁ type, subsequent T ₂ type, late T ₁ type
9	Davenport Blumenthal and Cantrell 1935	32 negro	A L V, at apex size of point of ice pick. Ant desc branch of lift cor artery and vein ligated	Yes	5 hrs P O	RT ₁ +1 mm RT ₂ +1 mm RT ₃ -2.5 (T ₃ invert)	2 days P O	RT ₁ +2 mm RT ₂ +1 RT ₃ -1 (T ₃ upright)	2 wks P O	T ₁ inverted T ₂ diphasic T ₃ upright	6 mos P O	Upright in all leads	Significant Q ₂ appears 5 hrs P O becomes smaller with time and R ₂ precedes it	Early T ₁ type, late T ₁ type
10	Davenport 1924	44 white	A R V in upper portion of middle third. Meas 5 mm. Interventricular branch of lift cor artery and vein ligated	?					19 days P O	Inverted in all leads	8½ mos P O	Upright in all leads	Small Q ₂ and Q ₃ appear in 1st tracing, present throughout	Late inversion of T in all leads
11	Purks 1931	18 negro	A R V, new interventricular septum. Desc branch of lift cor artery ligated in its middle third	Yes	10 min P O	RT ₁ +1 mm RT ₂ isoelectric RT ₃ -1	2 days P O	RT ₁ +3 mm RT ₂ +3 mm RT ₃ +5 (T ₃ inverted)	16 days P O	T ₁ inverted T ₂ slightly inverted T ₃ upright	2½ mos P O	Upright in all leads	Small Q ₂ and Q ₃ present 2nd day. Diminished in size later but varying in size from time to time	Initial T ₁ type, subsequent T ₂ type, late T ₁ type
12	Elkan and Phillips 1931—Case 1	18 negro	A R V Desc branch of lift cor artery ligated	Yes	10 min P O	RT ₁ +1 mm RT ₂ isoelectric RT ₃ -1	1½ days P O	RT ₁ +3 mm RT ₂ +3 mm RT ₃ +1 (T ₃ diphasic)	16 days P O	T ₁ inverted T ₂ and T ₃ upright	3 mos P O	Upright in all leads	Small Q ₂ and Q ₃ present throughout	Initial T ₁ type, subsequent T ₂ type, late T ₁ type
13	Schomknecht 1931	21 white	A R V Meas 2 to 3 cm long. Ant desc branch of lift cor artery ligated				1 EKG 7 days P O	Elevated in all leads greatest in Lead II	21 days P O	T ₁ and T ₂ inverted T ₃ small but upright			Significant Q ₃ present at 7 days absent at 14 days, present at 21 days	Early T type, late T ₁ type. Death in 4th week. Autopsy showed ant left ventricular infarction and beginning aneurysm formation

TABLE I (Continued)

Patient	Sex	Age	Race	P.O. (days)	Initial RT Changes		Subsequent RT Changes		T-Wave Inversion		T-Wave Return to Normal		Q-Wave Changes If Any	Comments
					Time	Nature	Time	Nature	Time	Nature	Time	Final Picture		
44	M	30	White	10		ARV, Mers 2 cm from apex, depth 1.5 cm, branch 1.5 cm, artery 1.5 cm	2 to 8 days P.O.	Inverted in all leads, greatest in lead II	16 days P.O.	T ₁ and T ₂ inverted, T ₃ upright but small	4½ mos P.O.	T ₁ still inverted, T ₂ and T ₃ upright	Small Q ₁ and Q ₂ persist throughout	Early T ₂ type, late T ₁ type
45	M	30	White	10		ARV, Mers 5 to 6 mm, branch 1.5 cm, artery 1.5 cm	9 hrs to 9 days P.O.	RT ₁ +1 mm, RT ₂ +2 mm, RT ₃ +1 mm	1 EKG 14 days P.O.	T ₁ and T ₂ inverted, T ₃ isoelectric	1 EKG 10 mos P.O.	Upright in all leads	None	Late T ₁ type
46	M	30	White	10		ARV, About 5 cm, above apex, Mers 1.5 cm, externally	3 days P.O.	T ₁ diphasic, T ₂ and T ₃ inverted	1 EKG 5½ mos P.O.	T ₁ diphasic and sig inv, T ₂ and T ₃ inverted	4½ mos P.O.	T ₁ isoelectric, T ₂ and T ₃ upright	Small Q ₂ and Q ₃ present on 1st day, gone by night, Small Q ₁ present on 33rd day, absent at 4½ months	Early T ₂ type, late inversion of T in all leads
47	M	48	White	10		ARV	3 days P.O.	T ₁ diphasic, T ₂ and T ₃ inverted	6 days P.O.	T ₁ upright, T ₂ diphasic, T ₃ sig inverted	3 mos P.O.	Upright in all leads	Small Q ₃ present throughout	Late inversion of T in all leads
48	M	22	White	10	12 hrs P.O.	RT ₁ +2 mm, RT ₂ +1 mm, RT ₃ +2 mm	1 to 9 days P.O.	Elevated in all leads	25 days P.O.	Inverted in all leads	5 mos P.O.	Upright in all leads	None	Early T ₂ type, late inversion of T in all leads, P.O. purulent pericarditis
49	M	16	White	10		ARV, middle third 1.5 cm to 1.5 cm, and parallel to ant. dec. branch of left coronary artery	1 EKG 3 days P.O.	RT ₁ +5 mm, RT ₂ +1 mm, RT ₃ +25 mm	1 EKG 15 days P.O.	Beginning of inversion of T ₁ and T ₂ , T ₃ inverted	1 EKG 4 mos P.O.	Upright in all leads	None	Early T ₂ type, late inversion of T in all leads

TABLE I (Continued)

Case No	Author, Year	Age, Color	Characteristics of Heart Wound	P O pericarditis	Initial RT Changes		Subsequent RT Changes		T-Wave Inversion		T-Wave Return to Normal		Q-Wave Changes If Any	Comments
					Time	Nature	Time	Nature	Time	Nature	Time	Final Picture		
21	Gissane and Schulenberg, 1937	23 white	A R V $\frac{3}{4}$ " to right of interventricular groove Meas. $\frac{3}{4}$ " P R V small wound	?			2 days P O	RT ₁ and RT ₂ elevated greatest in Lead II RT ₂ isoelectric (T ₂ inverted)	21 days P O	Inverted in all leads	5 mos P O	Upright in all leads	Rt axis deviation throughout Q ₃ significant in first 2 tracings, small in 3rd	
22	Matth, 1938	24 white	A L V, at base and close to obtuse margin, small slit-shaped opening P L V, at base of ventricle and near obtuse margin small wound Desc branch of circumflex branch of left coronary artery ligated	Yes	1 day P O	RT ₁ and RT ₂ elevated greater in Lead I RT ₂ slightly depressed	2 days P O 4 days P O	RT ₁ and RT ₂ same RT ₂ isoelectric RT segments as above (T ₁ slightly negative)					Significant C ₁ throughout	Died on 7th P O day Autopsy showed fibrinous pericarditis Infarct on the border of left ventricle between ant and post wall meas 5 cm vertically and 3 cm horiz
23	Mondry, 1939	30 white	A R V Meas 3 cm long A L V, near left margin Meas 3.5 cm P L V, small circular wound No arteries ligated				2 days P O	RT ₁ and RT ₂ elevated equally RT ₂ isoelectric (T ₂ isoelectric)	20 days P O	T ₁ and T ₂ inverted T ₃ diphasic	6 mos P O	Upright in all leads	None	

version of the T-waves This appears to substantiate the interpretation here presented

Those patients with wounds of the anterior right ventricular wall close to the interventricular septum with ligation of the descending branch of the left coronary artery showed a late T_1 type of tracing, probably because the bulk of the muscle in the infarct of the anterior left ventricular wall was much greater than that damaged in the injury of the right ventricle itself There was one exception, case 10, which had inverted T-waves in all leads

T-wave inversion in Leads I and II in anterior left ventricular injury, and inversion in all leads in right ventricular injury was also found by Paul Wood¹¹ in 1937, when he reviewed 13 cases of stab wounds of the heart and added one of his own However, he attributed the picture in cases involving the left ventricle to myocardial injury and in cases involving the right ventricle to hemopericardium Since hemopericardium occurs in injuries to either ventricle, it is difficult to see how it could be responsible for the electrocardiographic behavior in the case of one and not in the case of the other

The conception here stated, therefore, is that the electrocardiographic alterations in the first week or 10 days following suture of a heart wound are due to pericardial inflammation which in most cases is of the serofibrinous variety The T-wave inversion which is found two weeks to a month later, we believe, represents late evidence of destruction of a localized area of the myocardium by the original traumatizing agent, subsequent suturing and infarction if a coronary vessel was ligated This view is in essential agreement with the conclusions of Barnes³⁰ regarding myocardial infarction complicated by pericarditis He reported a number of cases, of which two came to autopsy, in which there was early RT elevation in all leads due to pericarditis Localization of the infarct in the anterior or posterior wall of the left ventricle was only possible on the basis of a distinctive Q pattern or T-wave inversion of the T_1 or T_2 type

Q-wave changes in the case reports here reviewed did not give any clue as to the location of the damaged muscle In some of the tracings small Q-waves, and in a few instances significant Q-waves, appeared in one or more leads They showed considerable variation in size from one electrocardiogram to the next, diminishing in size in some and increasing in size in others as time went on These Q-waves were probably due to change in position of the heart, because of manipulation at operation and because of postoperative effusions and adhesions in the pericardium and pleura

To refer back again to the RT segment changes in the first week, it might be asked what the picture would be if pericarditis were not present or did not produce electrocardiographic alterations, which it does not do in every case³⁰ Where the anterior wall of the left ventricle is involved, elevation in Lead I and depression in Lead III of the RT segment would be expected Such curves have been encountered early (from 10 minutes to 28 hours after operation) in four cases (5, 8, 11 and 12) They were evanescent and

rapidly superseded by RT elevation in all leads. In two additional cases (2 and 9) no clean-cut T_2 curve occurred at all, and the T_1 picture persisted throughout. Whether all injuries of this type would show a T_1 curve if the electrocardiograms were taken soon enough after operation is not known. In isolated anterior right ventricular injury no initial RT picture could be differentiated from that due to pericarditis, and it may be that the deviations are in the same direction as those due to pericarditis.

The three cases with multiple heart wounds also showed the T_2 type of curve early. The later findings represent a summation of electrical changes produced by the several areas of myocardial damage.

The case reported by us differs from all the others in that no T-wave inversion occurred at any time. Case 18 was similar in that the T-wave inversion was early and transient. In neither case was there electrocardiographic evidence of myocardial injury. The muscle lesions may not have been situated in the plane of the conventional leads, or they may have been too small to produce electrocardiographic changes.³¹

In order to verify or disprove these views on the electrocardiogram in penetrating wounds of the heart, many more case reports with early and repeated tracings will be necessary. It is also hoped that the location and extent of the injury to the heart will be carefully noted at operation and that postmortem studies of the existing pathological processes be made whenever possible in patients who do not survive.

SUMMARY

1 Twenty-two cases of stab and gunshot wounds of the heart with electrocardiographic tracings have been collected from the literature, and another case report of a penetrating wound of the left ventricle is added.

2 The sutured wound of the heart wall is a localized area of myocardial injury, necrosis and cicatrization. Ligation of a coronary vessel, generally the descending branch of the left coronary artery, is a frequent complication. Serofibrinous pericarditis occurs in almost all cases postoperatively.

3 In injuries involving the anterior wall of the left ventricle or arteries supplying this region, electrocardiograms taken from several minutes to a number of hours after operation may show the T_1 type of picture with elevation of the RT segment in Lead I and depression in Lead III. These changes are generally superseded after the first day by electrocardiographic modifications due to pericarditis, but occasionally persist.

4 During the first week the electrocardiographic picture is that of pericarditis regardless of the location of the wound or whether a coronary artery is ligated. There is elevation of the RT segment in the first two leads or in all three leads, generally most marked in Lead II. This is called the T_2 type of tracing.

5 From two weeks to one month after operation, T-wave inversion is

fully developed, and may last from two to six months or more before reverting to normal. In anterior left ventricular injury, the inverted T-waves are in Lead I or Leads I and II. In anterior right ventricular injury, the T-waves are inverted in all leads. It is probable that these late T-wave changes are characteristic of localized myocardial necrosis and scar formation in these respective regions.

6 The present case report of a penetrating wound of the obtuse margin of the base of the left ventricle showed a T_2 type of picture during the first 10 days. No inversion of T-waves followed. The electrocardiographic picture was that of pericarditis. The myocardial lesion was "silent" either because it was small, or because it was not in the plane of the conventional leads. Similar electrocardiographic findings were present in Davenport and Markle's case, which, however, was a wound of the right ventricle.

BIBLIOGRAPHY

- 1 DAVENPORT, G L. Stab wound of the heart, *Jr Am Med Assoc*, 1924, lxxxii, 1840
- 2 KOUCKY, J D, and MILLES, G. Stab wounds of the heart, *Arch Int Med*, 1935, lvi, 281
- 3 VANDER VEER, J B, and NORRIS, R F. The electrocardiographic changes in acute pericarditis, *Am Heart Jr*, 1937, xiv, 31
- 4 HESSE, E. The functional results of wounded and sutured hearts in the light of after-results of heart suture, *Deutsch Ztschr f Chir*, 1925, cxc, 239
- 5 BECK, C S. Wounds of the heart, *Arch Surg*, 1926, xiii, 205
- 6 BARNES, A R, and MANN, F C. Electrocardiographic changes following ligation of the coronary arteries of the dog, *Am Heart Jr*, 1932, vii, 477
- 7 FOWLER, W M, RATHE, H W, and SMITH, F M. The electrocardiographic changes following the ligation of the small branches of the coronary arteries, *Am Heart Jr*, 1933, viii, 370
- 8 SCHLOMKA, G. Electrocardiographic observations in stab wound of the heart, *Deutsch med Wchnschr*, 1931, lvii, 630
- 9 MATTI, H. A case of gunshot wound of the heart with ligature infarct, *Schweiz med Wchnschr*, 1938, lxviii, 611
- 10 VANDER VEER, J B, and NORRIS, R F. The electrocardiographic changes in acute pericarditis, *Jr Am Med Assoc*, 1939, cxiii, 1483
- 11 WOOD, P. Electrocardiographic changes of a T_2 pattern in pericardial lesions and in stab wounds of the heart, *Lancet*, 1937, ccxxxiii, 796
- 12 BARNES, A R, and BAYL, R G. The incidence and situation of myocardial infarction in one thousand consecutive post-mortem examinations, *Am Jr. Med Sci*, 1932, clxxxiii, 215
- 13 HYMAN, A S, and FISHER, J L. Post-traumatic disturbances of the heart, *Am Heart Jr*, 1926, ii, 61
- 14 BATES, W, and TALLEY, J L. The electrocardiograms of coronary occlusion following a stab wound in the left ventricle, *Am Heart Jr*, 1929, v, 232
- 15 ELFIN, D C, and PHILLIPS, H S. Stab wounds of the heart, electrocardiographic studies of two cases, *Jr Thoracic Surg*, 1931, i, 113
- 16 HOFFMANN, K. A healed heart wound, 1935 (Taken from P. Wood II)
- 17 KIRKLE, F. Electrocardiographic observation in bleeding heart wound, *Ztschr f Kreislaufforsch*, 1938, xxx, 466
- 18 PETERS, W B, and BLOOM, I A. Accidental stab wounds of the ventricle, *Am Jr Med Sci*, 1932, clxxxii, 79

- 19 DAVENPORT, G I, BLUMENTHAL, B, and CANTRIL, S Electrocardiographic studies of a stab wound of the heart, *Jr Thoracic Surg*, 1935, v, 208
- 20 FISCHER, L Heart wound and electrocardiogram, *Arch f klin Chir*, 1937, clxxxviii, 557
- 21 ANGELI, A A successful case of suture of heart wound caused by revolver bullet, *Arch Ital di Chir*, 1938, xlviii, 665
- 22 PURKS, W K The electrocardiographic findings following ligation of descending branch of the left coronary artery in man, *Am Heart Jr*, 1931, vii, 101
- 23 RAMSDELL, E G Stab wounds of the heart, *Ann Surg*, 1934, xcix, 141
- 24 DAVENPORT, G L, and MARKLE, P The electrocardiogram in stab wounds of the heart, *Jr Thoracic Surg*, 1934, iii, 374
- 25 WARTHEN, H J Stab wound of the heart, *Ann Surg*, 1935, cii, 147
- 26 GISSANE, W, and SCHULENBERG, B A penetrating stab wound of the heart, *Lancet*, 1937, ccxxxiii, 132
- 27 MONDRY, F The electrocardiogram in multiple heart wounds, *Zentralbl f Chir*, 1939, lxvi, 743
- 28 CRAWFORD, J H, et al Localization of experimental ventricular myocardial lesions by the electrocardiogram, *Am Heart Jr*, 1932, vii, 627
- 29 ROBB, J S, and ROBB, R C Localization of cardiac infarcts in man, *Am Jr Med Sci*, 1939, cxcvii, 7
- 30 BARNES, A R Electrocardiographic pattern observed following acute coronary occlusion complicated by pericarditis, *Am Heart Jr*, 1934, ix, 734 •
- 31 WOOD, F C, and WOLFERTH, C C Experimental coronary occlusion, *Arch Int Med*, 1933, li, 771

TACHYCARDIA AND SENSITIVITY TO HEAT AS INDICATIONS FOR BASAL METABOLIC RATE DETERMINATION *

By ABE RAVIN, M D , *Denver, Colorado*

SINCE the principal function of the thyroid is to increase the oxidative processes in the body, patients with hyperthyroidism show an increase in their basal metabolism. Recognition of this fact by the medical profession has resulted in some abuse of a diagnostic procedure which should supplement and not replace clinical diagnosis. In recent years records in the Out-Patient Department of the Colorado General Hospital show that the number of basal metabolic rate determinations requested has mounted greatly without a corresponding increase in the percentage of abnormal tests. A study was undertaken, therefore, to determine if some physical sign or symptom of hyperthyroidism occurred with sufficient frequency to justify its use as a practical indication for the time consuming basal metabolic rate determination, or if the absence of some physical sign or symptom justified omitting a basal metabolic rate determination.

TABLE I

Year	Number of Basal Metabolic Rate Determinations	Number of Chemical Determinations on the Blood
1932	541	630
1933	605	795
1934	548	781
1935	350	636
1936	266	725
1937	360	921
1938	408	765

METHODS

One hundred and forty-six patients from the Medical Out-Patient Department upon whom 150 consecutive basal metabolic rate determinations were performed constitute the material for this study. The patients were seen by many different physicians on the Staff. The physician recorded the lowest pulse rate obtained after the patient had been lying down for 10 minutes, the blood pressure, the size of the thyroid, the presence or absence of eye signs and tremor, subjective sensitivity of the patient to heat and cold, and changes in weight. Almost all the patients had had breakfast and had come some distance to the Clinic.

The patient, fasting since eight o'clock of the previous night, returned in one to several days for the basal metabolic rate determination. After the patients had rested for one hour in bed, the determinations were done in duplicate with a McKesson Metabolator. The pulse rate was counted several times during the determination and the *lowest pulse rate obtained and not the average pulse rate* was used in this work. Bierring standards were used for the boys from 13 to 18½ years, Boothby and Sandiford standards for girls from 13 to 18½ years, and Aub and Dubois standards for men and women over the above ages.

The subsequent clinical course of the patients was followed until a definite diagnosis was established, in the course of which many of the patients had repeated basal metabolic rate determinations.

RESULTS

Since examination of the data at once revealed the importance of pulse rate and sensitivity to cold, the cases were analyzed solely on the basis of these two factors. A marked correlation between the basal pulse rate and the basal metabolic rate has been found by many workers. We were, however, more interested in determining the lowest pulse rate level associated with elevated basal metabolic rates or, more exactly, with hyperthyroidism. Since the initial diagnosis of hyperthyroidism must be made in the out-patient clinic or office, we were especially interested in the pulse rate as determined in the clinic. Clinic pulse rates are influenced by several factors in addition to those acting on basal pulse rates and therefore have not been used previously for correlation with basal metabolic rates. As a result of the influence of exercise, food, and excitement, the clinic pulse rates may be expected to be higher than the basal pulse rates and to show greater variation. Since only the lower level of pulse rates associated with abnormally elevated basal metabolic rates was desired, it was felt worthwhile to use the clinic pulse rates in the hope that the smallest increment produced by exercise, food, and excitement would be fairly constant. A comparison of the clinic and basal pulse rates for all cases is shown in table 2. Since only 28 of the patients were men, no attempt was made to separate the sexes, and the figures are essentially those to be expected in women. It is interesting to

note that only after the pulse rate in the clinic exceeds 95 does the basal pulse rate show an increase over what may be considered a normal level of 70 to 75

Examination of the data revealed that basal metabolic rates over plus 15 were present in only two patients with basal pulse rates under 81. One of these patients, a 59 year old woman who complained of nervousness and poor appetite, had a basal metabolic rate of plus 24. Another basal metabolic rate done before the patient had received any treatment and at a time when the patient said she was feeling worse, was plus 1. The other patient, whose basal metabolic rate was plus 16, had asthma and had been diagnosed as being psychoneurotic. Other basal metabolic rates obtained on this patient were plus 5 and plus 14. Since neither of these patients was thyrotoxic the conclusion may be drawn that in this series no patient with hyperthyroidism had a basal pulse rate under 81.

TABLE II
Relation of Pulse Rate in Clinic to Pulse Rate During Basal Metabolic Rate Determination

Number of Cases	3	0	10	10	10	23	20	18	13	5	20	3	3	1	7	4
Pulse Rate in Clinic	46 to 50	51 to 55	56 to 60	61 to 65	66 to 70	71 to 75	76 to 80	81 to 85	86 to 90	91 to 95	96 to 100	101 to 105	106 to 110	111 to 115	116 to 120	Over 120
Average Pulse Rate during BMR	55	0	60	60	69	69	71	72	76	74	84	82	94	86	94	112
												88		93		

Basal metabolic rates over plus 15 were present in only four patients with clinic pulse rates under 96. Two of these four were the two patients described above. The other two were definitely thyrotoxic. One of these had a basal metabolic rate of plus 34 and a clinic pulse rate of 90. The clinic pulse rate on two other occasions was 104 and 96. The other patient was receiving Lugol's solution and showed a marked variation in her condition. Her pulse in the clinic at a time when she felt very well was 69, two days later her basal metabolic rate was plus 53 and her basal pulse rate 83. On her return to the clinic her pulse rate was 96 and it was evident that she had had a relapse since her previous visit. In this group of patients then, a clinic pulse rate of 96 appeared to be a good lower level for the pulse rate of patients with hyperthyroidism.

On examining the histories of all patients with pulse rates over 95 in the clinic, it was found that the patients could be divided into the following three groups: (1) a group with basal metabolic rates over plus 15 (table 3), (2) a group in which the basal metabolic rate was normal and in which organic disease of some nature—tuberculosis, other infections, cardiac disease—was present to account for the increased pulse rate, (3) another group composed of patients in whom the basal metabolic rates were normal but who had no organic disease to explain the symptoms which were in some

ways suggestive of hyperthyroidism (table 4) The surprisingly large number of patients in Group 3 (table 4) in whom the diagnosis of psychoneurosis was made and the preponderance of women are points worthy of emphasis Because these patients have many symptoms suggestive of hyperthyroidism, they must be distinguished from the patients in Group 1 (table 3) The clinic pulse rates were high in both groups, but a definite

TABLE III
Cases with Clinic Pulse Rates Over 95 and Basal Metabolic Rates Over +15

BMR	Clinic P R	BMR P R	HIC*	Age	Sex	Remarks
+84	148	144	C	36	M	Definite clinical hyperthyroidism
+64	140	116	I-C	49	F	Definite clinical hyperthyroidism
+57	118	116	C	46	F	Definite clinical hyperthyroidism
+57	108	96	C	40	M	Definite clinical hyperthyroidism
+48	110	120	C	43	F	Definite clinical hyperthyroidism
+36	120	84	C	42	F	Hypertension Chronic nephritis Psychiatric diagnosis of schizophrenia Gaining weight Probably a polyglandular dyscrasia
+21	120	84				
+34	96	86	C	21	M	Myeloid leukemia
+31	96	120	C	57	F	Adenoma of thyroid with symptoms of hyperthyroidism Hypertension and some signs of decompensation
+28	100	92	C	16	F	Definite clinical hyperthyroidism
+22	100	88	C	38	M	Definite clinical hyperthyroidism
+19	112	86	C	58	F	Diabetes mellitus with some symptoms of hyperthyroidism
+18	100	82		23	F	Bronchial asthma Slight fever at time BMR was taken Repeat BMR two months later -3
+17	120	96	H	54	M	C N S lues Heart enlarged Aortic systolic murmur

* H = Patient prefers heat

C = Patient prefers cold

I = Patient is indifferent to heat and cold

tendency for higher pulse rates existed among those with increased basal metabolic rates During the basal metabolic rate determination the pulse rate fell in both groups In the group with elevated basal metabolic rates the pulse rate fell from an average of 113 in the clinic to 101 during the basal metabolic rate determination In no case did the basal pulse rate fall below 81 In the group with normal basal metabolic rates the pulse fell from 103 to 82 In this latter group many basal pulse rates were below 81, but it is important to note that probably as a result of excitement the basal pulse remained quite high in many patients

It is evident that in the group of patients in whom the differentiation from hyperthyroidism is important the pulse rate may frequently be misleading. This is especially true of the pulse rate in the clinic but also true to a less extent of the basal pulse rate. Comparison of tables 3 and 4, how-

TABLE IV

Cases with Clinic Pulse Rates Over 95 and Basal Metabolic Rates of +15 or Under
Organic pathology not sufficient to account for increased pulse

BMR	Clinic P R	BMR P R	IIC	Age	Sex	Remarks
+10	100	86	I	23	F	<i>Psychoneurosis</i> —tension state with anxiety attacks
+ 8	100	94				Markedly labile pulse Psychiatric consultation with improvement
+ 7	100	80	I-C	40	F	Depression with some anxiety features Psychiatric consultation with improvement
+ 5	116	92	I-H	54	F	Nervousness and insomnia Impressions Hypertension <i>Psychoneurosis</i>
+ 3	105	82	I	35	F	Anxiety state with tension <i>Psychiatric consultation</i>
+ 3	104	68	H	32	F	Colloid goiter Nervousness Impression <i>Psychoneurosis</i>
+ 1	120	106	I	42	F	Marked nervousness and tension No organic pathology determined
+ 1	100	104	I-C	36	F	Complaint of nervousness Impressions Non-toxic adenoma of the thyroid <i>Psychoneurosis</i> —Improvement with psychotherapy
- 5	100	84	H	38	F	Pain in left side Menopausal symptoms
- 5	108	66	C	18	F	No definite diagnosis Continuation of pain in right lower quadrant following appendectomy with no objective findings
- 6	96	68	H	44	F	Substernal feeling of pressure, palpitation, vague pains, "sick headaches" No objective heart findings
- 7	96	88	I	29	M	Nervousness and palpitation <i>Psychoneurosis</i> —Improvement with psychotherapy
-10	100	72	I	31	M	<i>Psychoneurosis</i> Psychiatric consultation
-12	100	75	I	31	F	Colloid goiter "Thyroid choking her" Impression— <i>Psychoneurosis</i>
-15	96	62	H	18	F	Tired, dysmenorrhea Taking thyroid gr 1 daily at time of BMR

ever, shows a marked difference in the subjective sensitivity to heat of these two groups. In every case where the basal metabolic rate was elevated a definite preference for cold existed, whereas the group with normal basal metabolic rates either had no preference or definitely preferred heat.

In summary it may be noted that in all but two cases, and even these were not complete exceptions, every patient with hyperthyroidism

had a clinic pulse rate over 95 and was sensitive to heat. These two facts served to separate the hyperthyroid patients from the great majority of patients in whom hyperthyroidism was suspected but not present.

DISCUSSION

The changes in the circulatory system in hyperthyroidism have usually been considered compensatory. The extra oxygen required by the cells is carried to the tissues by an increase in the total blood flow. Since the total blood flow varies with the heart rate and the output of each cardiac contraction, attempts have been made by Read,¹ Gale and Gale,² Jenkins³ and Read and Barnett⁴ to find formulae for the prediction of basal metabolic rate from pulse rate and pulse pressure. Opinion as to the value of these formulae has varied, but the general opinion was expressed by Comroe⁵ when he stated that "the basal metabolic rate cannot be predicted from pulse rate and pulse pressure with sufficient accuracy and consistency to render the method a substitute for measurement by indirect calorimetry."

Since the total blood flow can be increased by merely increasing the output of each cardiac contraction, it would appear possible to have mild hyperthyroidism without elevation in heart rate. Increase in heart rate, however, according to recent work, may have another origin. The isolated perfused hearts of rabbits which have received thyroxin before death have been shown to continue to beat at an accelerated rate.⁶ This increase in the rate of pulsation was shown by Markowitz and Yater⁷ to be present in tissue cultures of fragments of heart muscle removed from chick embryos before the appearance of nerve elements in the heart. On the basis of these findings Yater⁸ says that "it appears that the increase in the rate of circulation is a fortuitous rather than a physiological adjustment. It is due mainly to the increase in thyroxin in the myocardium which causes the heart to beat more rapidly and vigorously."

The rapid pulse takes on renewed significance. The heart rate in hyperthyroidism should always be greater than normal. The only true exception to an increased heart rate in hyperthyroidism occurs when the heart for some reason is refractory to the action of thyroxin. Since other tissues of the body are sometimes apparently refractory to thyroxin, this occurrence is possible but certainly cannot be common. An increased heart rate may apparently be absent when the normal rate is so low that the increase resulting from hyperthyroidism is not evident. Sturgis and Tompkins⁹ followed a few patients with hyperthyroidism and apparently normal pulse rates and found that after thyroidectomy the pulse rates decreased to very low normals. The pulse rate, like the basal metabolic rate, may be normal during periods of spontaneous remission or during remission produced by iodine. In the presence of auricular fibrillation the pulse rate cannot be evaluated and the presence of this complication should not be overlooked.

The results given above indicate that the basal pulse rate in patients

with hyperthyroidism is usually above 80. The pulse rate will be higher in the clinic because of the effect of exercise, food, and excitement. Exercise produces an excessive increase in oxygen consumption and heat production in patients with hyperthyroidism¹⁰ and might, therefore, be expected to increase the pulse excessively. The specific dynamic action of food in hyperthyroidism has been found to be normal by some investigators, increased by others^{11, 12}. Because of an increased sensitivity to adrenalin and from the nature of their disease thyrotoxic patients might be expected to react excessively to excitement¹². The three factors of exercise, food, and excitement appear therefore to operate to increase the basal pulse of the thyrotoxic patient to a greater extent than that of the normal person. From the data collected it appears that the increase in the basal pulse rate as a result of these factors is at least 15; so that 96 serves as a good lower limit for the pulse rate of thyrotoxic patients in the clinic.

Because their symptoms resemble those produced by hyperthyroidism, the patients with normal basal metabolic rates and with no evident organic disease to account for their symptoms are often incorrectly thought to be thyrotoxic. When the cardiovascular complaints are conspicuous the diagnosis of "effort syndrome," "irritable heart," or "neurocirculatory asthenia" is often made. Billings¹³ found that almost half of these patients, whom he labels as having an "anxiety syndrome," were for varying periods of time incorrectly diagnosed and unsuccessfully treated for hyperthyroidism. Although a careful history, especially from a psychiatric standpoint, and a complete physical examination will usually establish the diagnosis, many can be separated from thyrotoxic patients merely by the presence of a pulse rate which is below 96 in the clinic and below 81 under basal conditions. Some of these patients, however, have rapid pulse rates under clinic conditions and, at times, even under supposedly basal conditions. Since the rapid heart rate is usually the result of a temporary decrease in vagal tone produced by psychic stimuli, diversion of the patient's attention results in an increase in vagal tone with slowing of the heart. A marked variation in the heart rate is therefore of value in recognizing these patients.

When the pulse rate fails as a guide, a difference in heat tolerance easily separates patients with anxiety syndromes from patients with hyperthyroidism. The thyrotoxic patient uses more oxygen and produces more heat. Under basal conditions this increase in heat production frequently amounts to 40 per cent of normal. This is approximately the heat produced by a normally active person. The thyrotoxic patient, however, not only starts from this elevated basal condition but shows an abnormal increase in his heat production in carrying out ordinary activity¹⁴. His heat production is not only that of a person doing moderately heavy or even very heavy manual labor. This is essentially true even in mild cases. All this heat must be dissipated, the greatest portion by radiation, convection and con-

duction Since the body loses heat more easily at lower environmental temperatures, these patients prefer cooler rooms and fewer clothes than normal persons To help dissipate the heat, the capillaries in the skin are dilated and the blood flow through them is greatly increased in quantity and velocity Loss of heat through evaporation from the skin is increased

Since the surface area of the extremities constitutes 65 per cent of the body surface, heat dissipation from the extremities is correspondingly important Maddock and Coller¹¹ found that the shift of blood to the surface of the body which results from an increase in body heat production is not uniform in all parts of the skin but is of much greater degree in the extremities than in the head and trunk The increase in skin temperature is, accordingly, greatest in the extremities They also found that the skin temperature of the great toes varied directly with the basal metabolic rate These findings explain why the hands and feet of the patient with hyperthyroidism feel warm both to the patient and to the examiner

Compare this condition with that which exists in the tense or anxious patient whose complaints and rapid pulse frequently make the differentiation from hyperthyroidism difficult Heat production and total cardiac output are normal The tension state frequently results in a spasticity of the vessels of the extremities, so that the blood supply is diminished and the blood flow sluggish Characteristically, these tense, anxious patients have cold hands and feet

In eliciting subjective sensitivity to heat, the question, "Do you like heat or cold better?" is as likely to receive a false as a true answer Sensitivity to heat or cold is more accurately discovered by questions such as the following "Do you like the house warmer or colder than the people around you?" "Do you use more or less bed covers than your husband?" "Are your hands and feet cold or warm?" "Do you now use less clothes in cold weather than previously?" A recent change in sensitivity is very important

In emphasizing the importance of tachycardia and sensitivity to heat, it is not intended to minimize in any way the importance of other symptoms and findings and a careful evaluation of all the information which can be obtained The practical value, however, of tachycardia and especially of sensitivity to heat for distinguishing the psychoneurotic from the thyrotoxic patients has been overlooked

SUMMARY

One hundred and forty-six patients have been studied from the standpoint of clinical diagnosis, pulse rate in the clinic, basal metabolic rate, pulse rate during the basal metabolic rate determination, and sensitivity to heat The following observations are made

The average basal pulse rate was not increased above the normal 70 to 75 level until the pulse rates in the clinic exceeded 95

Hyperthyroidism was uncommon with a pulse rate in the clinic under 96 and a basal pulse rate under 81

Patients with increased basal metabolic rates showed a definite tolerance to cold and sensitivity to heat which was important in distinguishing them from the psychoneurotics with whom they are most apt to be confused. The latter show either an indifference to heat or cold or a preference for heat.

CONCLUSIONS

1 If the pulse rate of a patient in the clinic is below 96, the patient probably does not have thyrotoxicosis

2 If the pulse rate of a patient in the clinic is below 81, the patient almost certainly does not have thyrotoxicosis and a basal metabolic rate determination is therefore unnecessary

3 If the patient expresses an indifference to heat and cold, thyrotoxicosis is probably not present

4 If the patient prefers heat or complains of cold hands and cold feet, thyrotoxicosis is almost certainly not present and a basal metabolic rate determination is unnecessary

I am indebted to Dr Robert C Lewis, Professor of Biochemistry, University of Colorado School of Medicine, and to the members of his department for doing the basal metabolic rate determinations and to Drs James J Waring, Robert S Liggett, and R S Ravin for their many helpful suggestions

BIBLIOGRAPHY

- 1 READ, J MARION Correlation of basal metabolism with pulse rate and pulse pressure, Jr Am Med Assoc, 1922, lxxviii, 1887
- 2 GALE, A M, and GALE, C H Estimation of the basal metabolic rate From formula based on pulse rate and pulse pressure, Lancet, 1931, i, 1287
- 3 JENKINS, R L Basal metabolism II The basal pulse complex, Arch Int Med, 1932, lxi, 189
- 4 READ, J M, and BARNETT, C W New formula for prediction of basal metabolism from pulse rate and pulse pressure, Proc Soc Exper Biol and Med, 1934, xxxi, 732
- 5 COMROE, BERNARD I Estimation of basal metabolic rate from pulse rate and pulse pressure, Am Jr Med Sci, 1935, cxc, 371
- 6 YATER, WALLACE M The tachycardia, time factor, survival period and seat of action of thyroxine in the perfused hearts of thyroxinized rabbits, Am Jr Physiol, 1931, xcvi, 338
- 7 MARKOWITZ, CECIL and YATER, WALLACE M Response of explanted cardiac muscle to thyroxine, Am Jr Physiol, 1932, c, 162
- 8 YATER, WALLACE M The mechanism of adjustment of the circulation in hyperthyroidism, Am Heart Jr, 1932, xiii, 1
- 9 STULTZ, CAROL C and TOMPKINS, EDNA H A study of the correlation of the basal metabolism and pulse rate in patients with hyperthyroidism, Arch Int Med, 1920, xxv, 46
- 10 PRINCE, H S, and BRIDGES, W M The cost of work in exophthalmic goiter, Am Jr Physiol, 1922-23, lxxv, 44
- 11 ROSS, HENRY The diseases of the endocrine glands, 3rd ed, 1935, William Wood & Company, Baltimore
- 12 HARRIS, J H The thyroid gland disease, 1937, J P Lippincott Co, Philadelphia
- 13 PRINCE, H S and GALE, A M Estimation of basal metabolic rate, 1937, xxvii, 14
- 14 HARRIS, J H and GALE, A M Estimation of basal metabolic rate in the clinic, 1937, J P Lippincott Co, Philadelphia

CLINICAL STUDIES WITH THE AID OF RADIO-PHOSPHORUS. IV THE RETENTION IN BLOOD, THE EXCRETION AND THE THERAPEUTIC EFFECT OF RADIO-PHOSPHORUS ON PATIENTS WITH LEUKEMIA *

By L A ERF, M D ,† L W TUTTLE, and J H LAWRENCE, M D ,
Berkeley, California

Previous studies ^{19, 20, 21, 22, 34, 35} have shown that radiophosphorus ($^{32}_{15}\text{P}$) (which owes its radioactivity to the spontaneous emission of beta rays) when administered in the form of sodium phosphate, at first concentrates in the bone marrow and those tissues infiltrated with leukemic cells and later concentrates in the osseous tissues. Radio-phosphorus has been used as a therapeutic agent during the past three years in all types of leukemia, with encouraging results. The principal advantages offered by radio-phosphorus appear to lie in its ease of administration (it may be given orally, intravenously, etc.), in its therapeutic effectiveness and in the fact that nausea, "radiation sickness" and other symptoms do not occur following its administration. This report deals with the rate at which P^{32} is absorbed into the blood and is excreted in the urine and feces of various patients and normal individuals, in addition to its therapeutic effectiveness in patients with leukemia. One hundred case studies are presented.

MATERIALS AND METHODS

A Radio-phosphorus

1 Production and quantitation

The radioactive phosphorus was produced by the Berkeley cyclotron ¹⁸. This instrument directs streams of very rapidly moving (16 Mev) deuterons (nuclei of heavy hydrogen) into ordinary red phosphorus (atomic weight, 31), and thereby converts some of it into radioactive phosphorus (atomic weight 32), which emits beta-particles only, with energies averaging 600,000 electron-volts and has a half-life of 14.3 days (i.e., at the end of a period of 14.3 days, one-half as many beta-rays are emitted as were being emitted at the start of the period). During bombardment the number of phosphorus atoms that become radioactive depends on the number and the energies of the striking deuterons. At present about one in every million atoms is made radioactive. This mixture of radio-phosphorus and inactive phosphorus is then converted into an aqueous solution of dibasic sodium phosphate.

* Received for publication May 7, 1941

Aided by a grant from the Blanche and Frank Wolf Fund of the University of California

† Wm R Kenan, Jr, Fellow

(Na_2HPO_4) of various concentrations (15 to 50 mg per c.c.) for oral and intravenous use. The amount of radiation emitted by the sodium phosphate solution depends upon the number of atoms of radioactive phosphorus present. When a sample emits 3.7×10^7 beta-particles per second it is said to contain one millicurie of beta-radiation. One microcurie is 1/1000 of a millicurie. Because of the innumerable factors which must be taken into consideration it is difficult to discuss this type of radiation in terms of "r" units with which the roentgenologist is familiar, but the radiations emitted by radio-phosphorus may be converted into "r" units by using the following equivalents: 1 microcurie = 37,000 beta-particles per second, 1 "r" = 1 e.s.u. of ions per cubic centimeter of air at S.T.P. The number of beta-particles multiplied by their average energy gives the total energy. This total energy, divided by the energy required to form one ion pair (about 32 eV) gives the number of ion pairs. Therefore the number of ion pairs formed by one microcurie of radio-phosphorus per second is equal to 37,000 (number of beta-particles) \times 600,000 (average energy of one beta-particle) divided by 32 (energy to form one ion pair) = 7×10^8 . To compare this with 1 "r" unit in water (or tissue) we must consider that 1 "r" unit in air = 1 e.s.u./c.c. = 2.1×10^9 ion pairs/c.c., the same dose of x-radiation in water produces an ionization greater than this by the ratio (density of water) divided by (density of air), or $2.1 \times 10^9 \times 800 = 1.7 \times 10^{12}$ ion pairs/c.c. Therefore 1 microcurie of radio-phosphorus contained in 1 c.c. of water produces an ionization in this volume equal to 7×10^8 divided by $1.7 \times 10^{12} = 4.1 \times 10^{-4}$ "r" units per second. The dose in one day is now obtained by multiplying this result by the number of seconds in a day (86,000), which gives the result

1 microcurie/c.c. of water physically equals approximately
35 "r" units, dosage per day

Thus, according to the above calculations, if a man weighing 50 kg. completely absorbed 1 millicurie of radio-phosphorus, and if these atoms are temporarily and evenly distributed throughout the body, he would be receiving in terms of roentgens the following calculated dose of irradiation for twenty-four hours

1 μ c (50 gm. body weight) = 1/50 μ c/gm. or c.c. of tissue
1/50 \times 35 = 35/50 or 0.7 "r" whole body irradiation in 24 hours

Since absorption is not complete, and since there is excretion and decay of P^{32} , the actual dose of irradiation decreases from day to day. Furthermore, the phosphorus atoms are not uniformly distributed and some tissues, such as bone marrow and tissues infiltrated with leukemia cells, receive by far the greatest amounts of irradiation.

The words "microcurie" or "millicurie" which appear throughout this paper refer to the number of beta-particles per second emitted by the solution

or tissue in question, as compared with a uranium standard (which emits 500 beta-particles per second), and not to standards emitting mixed radiations (alpha, gamma and beta) such as radium

2 Dosage

After the solution of dibasic sodium phosphate has been assayed for radioactivity, it may be administered by several routes. The most convenient is, of course, the oral route. The solution is mixed with equal parts of orange juice and is administered to the patient before breakfast.⁸ It may be given intravenously, intraperitoneally, subcutaneously, intramuscularly, directly into tumors, or as an unction.

Single oral doses have varied from 1 to 20 millicuries, depending on the age of the patient and the type of the disease, single intravenous doses have varied from 0.5 to 6 millicuries. Less than 3 grams of sodium phosphate have been administered orally in each dose, less than 1 gram when given intravenously. Two factors especially have governed the dosages administered to the patients reported in this paper. First, tolerance of patients to irradiation of any kind varies markedly so that the first doses given were always small. Second, the concentration of radiation had to be kept at a level which would do only minimal damage to the normal cells of the body. The first doses administered were determined by the following considerations:

a The lethal dose of radio-phosphorus for a 20-gram mouse is approximately that amount given intraperitoneally which emits 70 microcuries of beta-radiation, for a 6-pound monkey, 7 millicuries by the same route. These results suggest that the lethal dose of radio-phosphorus for an average adult human would be well over one hundred millicuries.

b By the Heublein technic⁴ as much as 20 "r" of x-radiation have been administered to the whole body daily for a period of three weeks' time to patients with various diseases.

Therefore the first doses of radio-phosphorus administered to adult patients were those which emitted between 1 and 5 millicuries of beta-radiation. The succeeding doses varied according to the clinical status and the levels of the red and white blood cells of the patient—the same guides used by roentgenologists.

Since the half-life of radio-phosphorus is but 14.3 days, there is no danger of cumulative radiation effects similar to those produced by such agents as radium or thorium which have half-lives of hundreds of years. Furthermore, from 25 to 50 per cent of a dose of radio-phosphorus is excreted by normal individuals during the six days after administration and 1 to 2 per cent daily thereafter. At that rate of excretion and considering the constant rate of decay, about 15 per cent of a dose would be retained at the end of two weeks. Six to eight weeks after a single administration of radio-phosphorus only insignificant amounts of radiation are found in any tissue, including the osseous tissues.⁵

Clinical Data Previous to Administration of Radio-Phosphorus

Phy and Lab Findings on Adm									Biopsy				
Name and Numbers	Sex and Age	Date of Admission	Chief Complaints and Duration of Chief Complaints on Admission	Diagnosis and Treatment Previous to Admission	Characteristics of Peripheral Lymph Nodes	Extension of Spleen Below Costal Margin in Cm	Extension of Liver Below Costal Margin in Cm	Other Findings	On Admission		M = Sternal Marrow L = Lymph Node R = Rib Marrow S = Skin Hyper = Hyperplastic	Chemistry and Serology, etc	Roentgenological Findings R = Rarefaction
1	2	3	4	5	6	7	8	9	Hb (%) Sahli	WBC/Cu mm in 1000's		13	14

TABLE I

Mr	M 43	5/27/40	Fracture external malleolus of right foot		Normal	None	None	Body weight 201 lbs	77	6		Wass - neg	
Pe	M 37	7/19/40	Fracture external malleolus of right foot		"	"	"	Body weight 154 lbs	85	8		Wass - neg	
Rob	M 31	3/25/40	Fracture radius of right arm		"	"	"	Body weight 141 lbs	93	7			
Vir	M 32	6/17/40	Wire (4.5 cm) foreign body removed surgically from right foot		"	"	"	Body weight 132 lbs	85	6		Wass - neg	

TABLE IV

Mr	M 40	2/ 6/35	Fatigue } 5 mo Anorexia } Cough } Abdominal pain } 3 wks	None No R	Small and shotty	1		Fundal hemorrhage and pallor	75	11	S lesion— no leukemia infiltration M—hyper (many monoblasts)	Wass neg	
Mr													

TABLE V

P22		Radia- tion	Transfusion		Phy and Lab Findings		Remis- sions	Postmortem Findings				P23 Studies			
Dates and Total Dosages of Radio-Phosphorus (in Millicuries) Adm O = Orally IV = Intravenously		X-Radiation or Neutron Radiation and Dates	Dates	Number	Total Amount of Blood in cc	LN = Lymph Node S = Spleen L = Liver I = Increased D = Decreased U = Unchanged Size Refers to Changes in	Min and Max Levels	Clinically and Hemato- logically Normal for a Period of 1 Year	General Condition of Patient on Mar 15, 1941	Date of Death	Hours Between Death and Autopsy	Gross Findings (Weight in Grams)	Microscopical Findings	Peripheral Blood = PB Excretions = E Tissue = T	Number
15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30

Normal Persons

7/22/40 1.5 (O)						76 to 77	6 to 7							P B E	1
7/22/40 1.5 (IV)						76 to 85	5 to 8							P B E	2
7/22/40 1.5 (O)						88 to 93	7 to 8							P B E	3
7/22/40 1.5 (IV)						84 to 85	6 to 7							P B E	4

Monocytoid Leukemia (Acute)

3/1/39 to 3/3/39 6.9 (O)									3/ 6/39	4	Gums swollen and ecchymotic Liver 2840, spleen 900 Bone marrow—red	Reticulo-endothelial hyperplasia of most organs including the kidneys and submucosa of GI tract	T	92
1/13/38 to 2/18/38 23.24 (O)									2/21/38	18	Gums edematous and ecchymotic Liver 2325, spleen 750 Marrow—red	Monocytoid infiltration lungs and heart kidneys adrenal, ovaries, breast, submucosa of GI tract gall bladder liver and hemopoietic organs	T	93

Plasmacytoid Leukemia (Acute)

a Lymphemic														
6/10/39 to 6/29/39 14.9 (O)		6/10/39 to 6/25/39	6	3000	LN—U S—U L—U	30 to 70	10 to 20		8/19/39	17	Liver 2720 spleen 760 Marrow—red	Plasma cell infiltration of most organs including marrow, kidneys and submucosa of GI tract	T	91

Non-Lymphemic

7/30/40 to 12/8/40 20 (O) 12/8/40 to 2/12/41 4.6 radio-strontium		11/7/40 to 3/1/41	2	1200	LN—U S—U L—U	50 to 77	1 to 4	Good (Pt being treated with radiostrontium)					P B E	9.
---	--	-------------------	---	------	--------------------	----------	--------	---	--	--	--	--	-------	----

Clinical Data Previous to Administration of Radio-Phosphorus

Phys and Lab Findings on Adm									Biopsy				
Name and Number	Sex and Age	Date of Admission	Chief Complaints and Duration of Chief Complaints on Admission	Diagnosis and Treatment Previous to Admission	Characteristics of Peripheral Lymph Nodes	Extension of Spleen Below Costal Margin in Cm	Extension of Liver Below Costal Margin in Cm	Other Findings	On Admission		M = Sternal Marrow L = Lymph Node R = Rib Marrow S = Skin Hyper = Hyperplasia	Chemistry and Serology, etc	Roentgenological Findings R = Rarefaction
1	2	3	4	5	6	7	8	9	Hb (%) Sahli	WBC/Cu mm in 1000's			

TABLE VI

a Myeloid (Associated with Neuroblastoma)

43 Pch	M 10 mo	11/7/39	Mass in upper right quadrant and in left supraclavicular region—3 mos	None No R	Left supraclavicular 3 cm in diam	7			85	13	L—neuroblastoma	NPN—10.5 Ca—9.7 Phos—5.8	mg 100 cc	R—most bones
--------	---------	---------	---	--------------	--------------------------------------	---	--	--	----	----	-----------------	--------------------------------	--------------	--------------

b Myeloid (Associated with Polycythemia)

67 Hc	M 20 yrs	2/11/40	Weakness Menstrual disorder Loss of weight (50 lbs) during previous 6 mos	21 yrs Leukemia March 1938 X-radiation	Shotty	24	6		110	55	M—hypernormal differential with 30% normoblasts	Sedimentation 1 mm/hr Wass.—neg		
-------	----------	---------	---	---	--------	----	---	--	-----	----	---	---------------------------------------	--	--

c Lymphoid (Associated with Leukemia)

54 Hc	M 21 yrs	1/6/41	General edema, ataxia Anemia Edema of lower extremities	Leukosarcoma with leukemia Dec 1940 No R	Generalized	1	1	Serotal edema	81	45	L—Lymphosarcoma			
-------	----------	--------	---	--	-------------	---	---	---------------	----	----	-----------------	--	--	--

d Myeloid (Associated with (24) Carcinoma of (100) Disseminated Tuberculosis)

100 Hc	M 41 yrs	1/1/41	Weakness and enlargement of the cervical nodes Nov 1940	Lymphosarcoma Nov 1940 Must X-radiation	Generalized	2	1	Protrusion of eyes and generalized edema	80	3	L—leukemic infiltration			
--------	----------	--------	--	---	-------------	---	---	--	----	---	-------------------------	--	--	--

Clinical Data Previous to Administration of Radio-Phosphorus

Phys and Lab Findings on Adm									Biopsy				
Name and Numbers	Sex and Age	Date of Admission	Chief Complaints and Duration of Chief Complaints on Admission	Diagnosis and Treatment Previous to Admission	Characteristics of Peripheral Lymph Nodes	Extension of Spleen Below Costal Margin in Cm	Extension of Liver Below Costal Margin in Cm	Other Findings	On Admission		M = Sternal Marrow L = Lymph Node R = Rib Marrow S = Skin Hyper = Hyperplastic	Chemistry and Serology, etc	Roentgenological Findings R = Rarefaction
1	2	3	4	5	6	7	8	9	Hb (%) Sthh	WBC/Cu mm in 1000's			

TABLE VI

Myeloid (Associated with Neuroblastoma)

Rich	M 10 mo	4/7/39	Mas in upper right quadrant and in left supraclavicular region—3 mos	None No R	Left supraclavicular 3 cm. in diam	7			85	13	L—neuroblastoma	NPN—49.5 Ca—9.7 Phos—5.8	R—most bones
------	---------	--------	--	--------------	------------------------------------	---	--	--	----	----	-----------------	--------------------------------	--------------

Myeloid (Associated with Polycythemia)

Hess	M 50	2-11-40	Weakness Mass in ab- domen Loss of weight (50 lbs) during previous 6 mos	Leukemia March 1938 Radiation	Shotty	21	6		110	55	M—hyper normal differential with 30% normoblasts	Sedimentation 1 mm/hr Wass—neg	
------	------	---------	---	-------------------------------------	--------	----	---	--	-----	----	--	--------------------------------------	--

Lymphoid (Associated with Leukosarcoma)

Mil	M 52	12-6-41	Generalized lymphadenopathy Aden- opathy of lower extremities	Leukosarcoma with leukemia Dec 1940 No R	Gen- eral- ized	1	1	Serotal edema	81	45	L—Lymphosarcoma		
-----	------	---------	---	--	-----------------------	---	---	---------------	----	----	-----------------	--	--

Myeloid (Associated with (90) Chloma and (100) Diffuse Marrow Tumor)

Case	M 11	1-1-41	Weakness Loss of weight Loss of appetite Loss of sleep	Leukemia Nov 1940 Mantle X-ray No R	Gen- eral- ized	2	1	Protrusion of eyes and supraclavicular subclavicular masses	80	3	L—leukemic infiltration		
------	------	--------	---	--	-----------------------	---	---	--	----	---	-------------------------	--	--

Case 11-1-41
Loss of weight
Loss of appetite
Loss of sleep

Case 11-1-41
Loss of weight
Loss of appetite
Loss of sleep

1. A. A. and V. I. (C. 4. 10. 10)

17c 111,000

Chemical Data after Administration of Radio-Phosphorus

History of Illness		Physical Examination		Postmortem Findings	
1	Chief Complaint	2	General Appearance	1	External Findings
2	Onset	3	Vital Signs	2	Internal Findings
3	Duration	4	Weight and Height	3	Microscopical Findings
4	Progress	5	Temperature	4	
5	Associated Symptoms	6	Heart and Lungs	5	
6	Previous Illnesses	7	Abdomen	6	
7	Family History	8	Neurological	7	
8	Patient's History	9	Other Systems	8	
9	Summary	10	Conclusions	9	

Lutened Reactions

2. We're still in the dark about the future of the program.

11-17-79 to 11-29-79 53 (0)	12-1-79 to 12-7-79 109 (1)	1X-1 5-6 1-1 (12 cm)	(S) 9 to (S) 16	12-8-79	1S	Neuroblastoma with generalized metastases in most organs	Typical micro- scopic findings
--------------------------------------	-------------------------------------	----------------------------	-----------------------	---------	----	---	--------------------------------------

1. What are the various types of information systems?

2 26/40 to 5/10/40 29 12 (O)	I N-U S-D (6 cm) I-D (2 cm)	110 to 115	15 to 53	Yes	Excellent					P
------------------------------------	-----------------------------------	------------------	----------------	-----	-----------	--	--	--	--	---

c Lymphoid (Associated with Leukocytes)

1/2/41 to 3/3/41 6.9 (I V) 7.5 (O)			Arteries and edema of legs entirely disap- peared	81 to 55	8 to 30	Excel- lent				
---	--	--	--	----------------	---------------	----------------	--	--	--	--

d Monocytoid (Associated with (90) Chloroma and (100) Diffuse Marrow Tuberculosis)

1/2/41 to 3/8/41 14 OS (I V) 17 (O)					LN—D S—not palpable L—not palpable Sub masses dis- appeared Pro- trusion of eyes unchanged	85 to 111	3 to 6			3/27/41	Liver and spleen normalsize kidneys and ad- renal sur- rounded with tumor All nodes 3X nor- malsize Retro- bulbar masses present	Liver—not infil spleen —fibroticmarked infil of heart, kidneys, adrenals GI tract pancreas, pituitary gland and brain Marrow—re- placed by round cells	
4/5/39 to 4/29/39 73 (O)					LN—U S—U L—U	50 to 59	12 to 24			6/ 6/39	6	Splenomegaly	Diffuse miliary tubercu- losis of peritoneum, spleen marrow, liver, adrenals lymph nodes but not lungs

TABLE II (Continued)

		M 67	1/13/40	1 Weakness 2 Necrotic gums	3 mo	A None B No B	(crystal mod + (2X))	2	1	Gums by p. r- phetic pit and necrotic Pallor	11	109			1/16/10 to 1/17/10 112 (O)				
10 Ric																			
11 Str		F 42	4/23/40	1 Weakness—3 mo		A None B No B	Shotty				37	32			1/23/10 to 5/22/10 50 (O)		1/23/10 to 1/28/10	2 1000	
12 Wel		F 40				A B									7/ 2/38 to 7/30/38 596 (O)				
13 Am		F 48	2/18/41	1 Tiredness 2 Diarrhea 3 Vomiting	2 mo	A Leukemia B No B		7			91	117			2/19/11 30 (O)				
14 Ben		M 45	5/ 6/40	1 Intermittent pain in upper left and lower right quadrant and headache	4 yr	A None B No B		8	1	Mx in right, lower quadrant	53	164	MI hyper (50% myelo- cytes)		5/22/10 to 9/25/10 87 (V) 1191 (O)				
15 Bram		F 45	4/28/39	1 Weakness 2 Loss of weight 3 Echinymosis 4 Enlarged abdomen	1 yr	A Leukemia B X-radia- tion 1750 r	General enlarge- ment	5		Pigmenta- tion of skin over splenic area	81	100			1/20/39 to 11/13/39 3501 (O)		12/ 8/39 to 12/28/39	1 2000	
16 Brat		F 21	7/20/38	1 Weakness—2 mo		A None B No B	Shotty	4		Pallor	63	195			7/20/38 to 9/ 8/39 1165 (O)				
17 Cole		M 23	5/23/40	1 Weakness 2 Diaphoresis 3 Abdominal pain 4 Headache	1 yr 2 mo	A None B No B	Postec- vical and axillary nodes Shotty	Not palp	Not palp	Slight gingivitis	81	148	MI hyper (myeloid)		5/27/10 to 1/ 8/41 190 (O)				
18 Cur		F 18	6/15/39	1 Weakness—3 yr 2 Fever 3 Bone pains 4 Night sweats	2 mo	A Leukemia B X-radia- tion Many courses		3		Pallor	30	470			9/ 6/39 to 9/16/39 1477 (O)		9/ 6/39 to 9/16/39	3 1500	
19 Ebe		M 39	1/20/39	1 Weakness 2 Night sweats 3 Headache	2 yr	A Leukemia B X-radia- tion 3 courses		3		Pallor	90	128			1/24/39 to 9/ 9/39 600 (O)		8/ 7/39 to 8/19/39 750 r	2 1000	
20 Flh		F 35	1/13/41	1 Fatigue 2 Headache 3 Diffuse joint pains	2 yr	A Leukemia B X-radia- tion 2/39 to 12/40 3000 r		2	0 5		82	186			1/14/41 to 1/31/41 67 (IV)				

TABLE II (Continued)

26 Hf	F 74	7/29/40	1 Weakness 2 Fatigue	A Leukemia B X-radia- tion 11/39 to 7/40 1000 r		6	3	Pallor	75	21	M hyper (myeloid in- filtration)	7/40/10 to 1/22/41 18.3 (O)				
27 Ken	M 21	11/ 4/38	1 Weakness—1 mo	A Leukemia B No R	Axillary nodes enlarged	8	1		70	210	M hyper (myeloid)	11/28/38 to 6/13/39 10.72 (O)				
28 Khl	M 31	5/13/40	1 Weakness 2 Loss of weight 3 Diaphoresis 4 Cramps in calves } 1 yr	A Leukemia B Dec 1939 X-radia- tion 1500 r	Shotty	1	1		76	103	M hyper (80% myeloid cells)	6/13/40 to 11/23/40 1.95 (IV) 17.0 (O)				
29 Kre	M 11	7/14/39	1 Weakness 2 Pain in groin 3 Fever } 3 mo	A Leukemia B May 1939 X-radia- tion 1000 r	Shotty	2		Petechiae in oral mucous membrane	57	115		7/14/39 to 2/ 1/41 28.0 (O)	10/ 7/39 to 11/15/39 800 r	7/14/39 to 2/ 1/41	5	2100
30 LaV	F 44	10/25/38	1 Weakness } 5 yr 2 Leukemids 3 Diaphoresis 4 Swollen ankles } 2 yr	A Leukemia B Sept 1935 X-radia- tion Many courses	Inguinal nodes enlarged (2 X)			(6/10/35 First admis 10/25/39 Second admis	75	208	M hyper (normal diff Dec 1939)	1/ 1/39 to 2/17/41 21.72 (O)				
31 Loh	M 33	7/21/38	1 Weakness 2 Abdominal pain 3 Splenic infarcts— Second admission	A Leukemia B Fowler's solution X-radia- tion 5000 r	General enlarge- ment (2 X)	6	5	Pallor Hemor- rhoids	40	117		8/ 1/38 to 8/20/38 15.87 (O)		8/ 2/38	1	51
32 Loo	M 46	10/16/40	1 Weakness 2 Loss of weight 3 Pain in upper abdomen 4 Bone pains in hands and attacks of diarrhea } 1 yr	A Leukemia B Feb 1940 X-radia- tion 1050 r	Shotty	Just palp	Just palp		92	77		10/16/40 to 2/18/41 25.4 (O)	R— bones of hands			
33 Mar	F 11	4/12/40	1 Tiredness—2 mo	A None B No R	Shotty	4			88	125	M hyper (myeloid)	4/13/40 to 2/19/41 17.17 (O)	R—all bones			
34 Mas	M 46	11/18/40	1 Weakness 2 Fatigue 3 Headache } 2 yr	A Leukemia B Sept 1938 X-radia- tion 3/11/39 to 9/17/40 2000 r	Shotty	6	Not palp		100	159		11/18/40 to 1/31/41 4.7 (IV) 8.7 (O)				

Chronic

TABLE II (Continued)

Case No.	Sex	Date of Birth	Admission Date	Chief Complaints	History	Physical Exam	Pathology	Diagnosis	Prognosis	Outcome
42 Smi	F 40	7/15/39	1 Weakness—2 yr 2 Swollen ankles—3 mo	Shotty	A Leukemia 1937 B X-radiation 3000 r	90	155			7/18/39 to 6/19/40 52 8 (O)
43 Smi	M 33	5/24/39	1 Weakness—2 yr		A Leukemia 1937 B X-radiation Many courses	92	380	MI hyper (myelocytes predominate)		5/31/39 to 2/12/40 64 15 (O)
44 Sor	M 61	5/13/40	1 Weakness—3 wks First admission		A Leukemia Aug 1937 B Fowler's solution X-radiation Unknown amounts	85	209			5/17/40 to 11/ 9/40 20 85 (O)
45 Tha	M 51	6/15/39	1 Weakness } 2 yr 2 Dyspnea } 3 Ankle edema }	Shotty	A Leukemia July 1937 B X-radiation Many courses	72	97			10/21/39 to 5/16/40 1 1 1 (V) 25 0 (O)
46 Tho	M 65	9/20/39	1 Weakness } 2 mo 2 Dyspnea } 3 Ankle edema }	General enlargement (2 X)	A Leukemia Aug 1939 B Fowler's solution	30	194	MI hyper (myelocytes predominate)	Wass—neg B V R (+12)	10/18/39 to 2/21/40 28 7 (O)
47 Wal	M 31	11/15/39	1 Periodic weakness for 23 mo	Shotty	A Leukemia Jan 1938 B Fowler's solution X-radiation Many courses	110	14			12/ 9/39 to 2/20/40 23 06 (O)
48 Wnt	M 42	12/17/38	1 Weakness—6 mo 2 Soft stools—4 yr 3 Pain in upper left quadrant—1 wk	Axillary nodes enlarged (3 X)	A Leukemia Feb 1938 B X-radiation 7000 r	52	256			3/17/39 to 5/ 3/39 35 77 (O)
49 Wtl	F 12	7/10/40	1 Pallor and purpura 2 Loss of weight } 5 mo 3 Hiccoughs and cramps in legs }		A Leukemia May 1940 B X-radiation 250 r	60	182	Skin and hair very dry		7/10/40 to 12/ 2/40 25 3 (O)
50 Ytt	F 40	8/27/40	1 Weakness 2 Deep boring bone pains in pelvis, back and sternum		A Leukemia Mar 1939 B X-radiation since Mar 1939	94	15			8/27/40 to 12/ 5/40 28 0 (O)

TABLE II (Continued)

[illegible]

TABLE II (Continued)

34 Mas	M 46	11/18/40	LN—U S—D (4 cm) L—U	100 to 78	148 to 53			Excel- lent					P B	34
35 Mon	M 37	6/27/40	LN—U S—U L—D (1 cm)	87 to 98	8 to 64	A		Excel- lent						35
36 Mor	F 38	9/18/38	LN—U S—U L—U	16 to 64	4 to 275	A 2 occasions	10/18/39		10	Liver—1900, spleen— 1100 Marrow red	Myeloid infiltration of many organs but not kidney or adrenals Infarct of spleen Myeloblastic hyperplasia of marrow	T	36	
37 Nut	M 57	5/ 3/40	LN—U S—D (4 cm) L—U	66 to 87	76 to 380			Excel- lent				T	37	
38 Pac	M 33	7/31/39	LN—U S—U L—U	65 to 70	12 to 138		9/11/39		12	Liver—2000, spleen— 2640 Marrow red and hyperplastic	Myeloid infiltration of all organs, except kidney and brain		38	
39 Par	M 51	5/14/40	LN—U S—D (1 cm) L—U	70 to 99	44 to 335			Good					39	
40 Pol	F 36	2/19/41	LN—U S—U L—U	93	23			Good					40	
* 41 Rov	M 52						9/28/38		18	Liver—2010, spleen—780 Marrow red and hyper- plastic, multiple white patches on pleura	Diffuse milky tuberculosis was ob- served Little leukemic infiltration microscopically	T	41	
42 Smi	F 40	7/15/39	LN—U S—U L—U	60 to 65	5 to 155	B	8/23/40						42	
43 Smi	M 33	5/24/39	LN—U S—I (20 cm) L—I (6 cm)	40 to 83	17 to 215	B	5/11/40			Spleen—455, liver—3310, kidneys—449 Bronchial nodes enlarged, soft, gray Many infarcts on spleen		T	43	
44 Sor	M 61	5/11/40	LN—U S—U L—U	30 to 80	169 to 640		11/13/40						44	
45 Thr	M 51	6/15/39	LN—U S—I (16 cm) L—U	45 to 63	6 to 97	A	6/13/40					P B L	45	
46 Tho	M 65	9/20/39	LN—U S—U L—U	27 to 35	9 to 184		3/23/40		2	Liver—2300, spleen—390 Marrow red and hyper- plastic	Myeloid infiltration of all organs ex- cept kidneys and pancreas Diffuse miliary tuberculosis involving lungs, liver, spleen and lymph nodes Marrow—myeloblastic hyperplasia	T	46	

Because of the findings obtained from absorption and autopsy studies, we feel at the present time that frequent administrations of small doses (0.5 to 2 Mc) of radio-phosphorus to patients with leukemia are preferable to infrequent large doses. It is known that radio-phosphorus can reach nearly every cell in the body and that it concentrates in those cells with active metabolic rates^{15, 20}. There is no evidence that cells can distinguish radio-phosphorus (atomic weight 32) from ordinary non-radioactive phosphorus (atomic weight 31). In tables 7 and 8 it can be noted that most of the doses given orally were of the same order of magnitude, and this was true with those given intravenously. The physiological function of normal cells was probably altered by these amounts of irradiation and therefore these doses are said to be "therapeutic" in nature, in contrast to "tracer" doses which are so small that the emitted radiation would not alter cellular physiology. Since the dosages of P^{32} administered to the normal individuals, myeloid and lymphoid leukemic patients were similar, the results in most instances can be discussed comparatively.

3 Tolerance

Radio-phosphorus is well tolerated by humans and animals. Multiple doses have been administered both orally and intravenously to over 300 persons with various disease processes and in none has there been any untoward reaction which might reasonably be ascribed to the radio-phosphorus, such as "radiation" nausea, vomiting, headache and weakness. One notable effect has been that of a marked increase in appetite for one or two days following the administration of radio-phosphorus.

B Patients

The cases reported, with one exception, are those of patients who were treated at the Crocker Radiation Laboratory or in hospitals near the Laboratory. The large number of patients who were treated elsewhere could not be followed closely and therefore are not reported at this time. The patients with leukemia were classified according to the predominating cell in the blood stream and to the acuteness or chronicity of the process. Most of the patients who were treated with radio-phosphorus had high white blood cell levels. Eight patients with leukemia, whose cases have been previously recorded^{20, 22, 25} are included in this report. The patients with leukemoid reactions are classified according to the primary etiological process. Through rare good fortune, studies on the rates of absorption and excretion of radioactive phosphorus were made on four healthy, robust normal men with recently healed fractures, all of whom had received the same type and quantity of food for a period of from one to eight weeks, and each of whom had a single regular bowel movement daily. These persons were particularly valuable because they all had had the same dietary phosphorus intake for weeks before, and during the period of study.

C Technic of Diagnosis and of Radioactivity Assays

57	Fré	M	8	11/23/40	1 Pallor 2 Weakness 3 No appetite 4 Attacks of vomiting, fever	1 mo	A Leukemia Oct 1940 B 3 transfusions	Gen enlargement shotty	2	2	67	10					11/21/40 to 11/29/40 20 (15)		10/21/40 to 2/23/41	6	2000
58	Gre	M	45	4/17/40	1 Weakness 2 Enlarged peripheral nodes 3 Diaphoresis 4 Dyspnea	2 mo	A None B No R	Gen enlargement (2 X)	1	8	17	11	1 Enlarged tonsils 2 Gen purpura				1/18/40 to 5/15/40 19 65 (O)		1/21/40 to 5/18/40	7	3500
59	Hier	M	4	7/12/40	1 Lethargy 2 Anorexia, pallor 3 Petechiae 4 Vomiting 5 Bleeding gums	5 mo 1 wk	A Leukemia April 1940 B No R	Gen enlargement (2 X)	6	3	28	15	1 Ecchymoses 2 Enlarged tonsils	Wass—neg Bl culture—non-hemolytic at 1 ph albus			7/11/40 2 (O)		7/12/40 to 7/26/40	1	1750
60	Kin	M	9	5/16/38	1 Weakness 2 Anorexia 3 Epistaxis 4 Bone pains	3 mo	A Leukemia Mar 1938 B 8 transfusions	Gen enlargement (4 X)	5	5	36	116	1 Pallor 2 L-pistaxis	Wass—neg	R—most bones		5/19/38 to 5/21/38 11 65 (O)		5/28/38 to 6/ 5/38	5	1320
61	Iud	M	23	12/19/40	1 Sore throat 2 Enlarged cervical nodes 3 Sternal pain	3 wks	A Leukemia Nov 1940 B 1 X-ray R	Gen enlargement (2 X) tender	1	7	39	400					12/20/40 to 12/21/40 6 99 (O)	12/27/40 100 r			
62	Rog	F	58	9/ 6/40	1 Weakness 2 Abdominal distention 3 Vomiting 4 Indigestion gas	1 mo	A None B Abdominal tap (8/25/40), 6 pts fluid withdrawn	Shotty firm	2		60	625	1 Ascites 2 Pdenr of thighs				9/15/40 6 6 (O)				
63	Rog	F	52	3/ 2/40	1 Weakness 2 Profuse perspiration 3 Loose stools 4 Ascites—6 mo	1 yr	A None B No R	Gen enlargement (2 X)	6	2	58	125	1 Ascites	Cell culture—blood lymphocytes grew readily			3/ 1/40 to 4/ 5/40 17 33 (O)				
* K 64	Snu	F	24														12/11/37 to 2/24/38 44 0 (O)				
65	Tul	F	27	7/23/40	1 Tiredness—1 yr 2 Pallor dyspnea 3 Abdominal pain 4 Petechiae 5 Bleeding gums	3 mo 1 wk	A None B No R	Gen enlargement (1 X) tender	4	2	66	104	1 Petechiae 2 Spine tender 3 Ecchymoses	Wass—neg Feces—pos Occult bl	R—most bones		7/25/40 40 (O)		8/ 1/40 to 8/12/40	5	2050
66	Wel	M	30	6/ 6/40	1 Swelling of lymph nodes 2 Dyspnea 3 Loss of weight	3 mo	A None B No R	Gen enlargement (4 X)	5		33	112	1 Petechiae 2 Hemorrhage in conjunctiva 3 Enlarged tonsils				6/25/40 to 6/28/40 9 1 (O)	6/25/40 to 7/ 1/40 3000 r	6/13/40 to 6/25/40	3	1500

TABLE III (Continued)

	F 50	8/30/40	1 Weakness 2 Pallor 3 Enlargement of 1 yr abdomen and of nodes	A Lymphoid leukemia Jan 1940 B No R	Gen en- largement (3 X)	20	2		10	%					8/30/40 to 2/5/41 25.0 (O)
72 Foo	F 70	4/16/40	1 Weakness—3 yrs	A Leukemia Mar 1937 B X-radiation	Gen en- largement (3 X)	5	5		61	1000					1/23/40 1.5 (I V) 4/21/40 1.7 (O)
73 Fra	F 47	4/23/40	1 Weakness } 2 Bruises } 3 yrs easily }	A Leukemia Jan 1937 B Fowler's solution	Gen en- largement (2 X)				97	101					1/29/40 to 1/22/41 4.5 (I V) 22.7 (O)
74 Gra	M 72	2/20/40	1 Weakness } 2 Anorexia } 6 yrs 3 Purpura }	A Leukemia 1934 B Fowler's solution, benzol. X-radiation	Gen en- largement (1 X)			1 Purpura on scro- tum and thighs	97	110	M--hyper (81% lympho- cytes)				2/21/40 to 3/18/41 59.75 (O)
75 Hor	M 66	7/6/39	1 Weakness 2 Enlarged abdomen 3 Swollen ankles 4 Bone aches	A Leukemia Jan 1939 B No R	Gen en- largement (3 X)	9		1 Heart enlarged 2 Leukemids of hands feet and abdomen	62	223		Wass —neg			8/18/39 to 1/3/41 1.8 (I V) 20.12 (O)
76 Lea	F 61	11/8/40	1 Weakness 2 Anorexia 3 Loss of weight 4 Diaphoresis	A Leukemia Sept. 1940 B No R	Gen en- largement (2 X)	20	15	1 Gen purpura	62	403		Wass —neg			11/16/40 2.6 (I V) 12/15/40 2.6 (I V)
77 Lyt	M 59	3/18/40	1 Weakness—1 yr 2 Enlargement of lymph nodes	A Leukemia Nov 1939 B Fowler's solution	Gen en- largement (2 X)				107	13		Wass —neg			3/23/40 to 9/27/40 23.0 (O)
78 Mil	F 61	9/30/40	1 Weakness } 2 Abdominal } 4 mo pain }	A Lymphoid leukemia Sept. 1940 B No R	Gen en- largement (2 X)	16	2	1 Purpura on both lower ex- tremities	44	114					9/30/40 to 12/27/40 28.35 (O)
79 Mic	M 55	10/25/38	1 Weakness } 2 Cough } 4 wks 3 Enlarged } abdomen }	A Leukemia July 1938 B X-radiation	Gen en- largement (2 X)	7	5	1 Pallor	44	423	M--hyper (90% lympho- cytes) L--lymphoid hyper	Wass —neg			2/9/39 to 3/9/40 59.42 (O)
80 Mic			4 Swollen ankles—1 wk												2/9/39 120 r (Heu- blein)

Page 11 (continued)

Statistical Data: Procedures to Administration of Radio-Phosphorus

[illegible]

TABLE III (Continued)

86 Sch	M 54	8/16/40	1 Weakness 2 Headache 3 Enlarged inguinal glands	1 wk	A Leukemia Sept 1940 B Fowler's solution transfusions	Gen enlargement (2 X)	2	2	1	Superficial abdominal veins distended	37	197	L—lymphoid infiltration		10/20/40 200 (O)		10/21/40 to 11/6/40	6	2350
87 Tay	M 49	11/2/39	1 Weakness 2 Mucoid stools 3 Sleepiness	6 mo	A None B No R	Gen enlargement (2 X)	6		1	Pallor	72	325	L—lymphoid infiltration	Wt's —neg	11/9/39 to 3/7/40 25.33 (O)				
88 Tod	M 45	11/14/40	1 Occasional weakness	1 yr	A Leukemia Oct 1939 B X-radiation	Gen enlargement (1 X)	1	2	1	Occasional toothache	110	70	M—hyper (lymphoid cells pre-dominate)		11/29/40 to 1/31/41 50 n				
89 Val	M 66	1/25/40	1 Gen lymphadenopathy 2 Weakness—1 mo	1 yr	A None B No R	Gen enlargement (2 X)	2	2			70	87		Wt's — ++ ++ ++	1/13/40 to 2/3/40 9.3 (O)				
90 Vol	F 72	3/9/39	1 Enlarged abdomen 2 Enlarged peripheral lymph nodes	1 yr	A None B No R	Gen enlargement (2 X)	8	2	1 2	Ascites Edema of ankles	42	119		Wt's —neg	3/17/39 to 4/6/39 12.24 (O)		3/17/39 to 4/6/39	2	1000
91 You	M 67	4/11/40	1 Enlarged glands 2 Fatigue—3 mo	10 mo	A Leukemia Jan 1940 B X-radiation (3360 r)	All nodes 1 cm in diam	6				95	66	M—hyper (48% lymphocytes)		4/12/40 2.16 (1 V) 4/23/40 to 1/20/41 24.0 (O)				

Clinical Data After Administration of Radio-Phosphorus

Radio-Phosphorus Studies																
Postmortem Findings																
Remissions																
Physical and Lab Findings																
Name and Number	Sex and Age in Years	Date of Admission	LN = Lymph Node S = Spleen L = Liver	Refers to Change in Size After Treatment That Round on Admission I = Increased D = Decreased U = Unchanged	Min and Max Levels		Patient Essentially Normal Clinically Associated with a Distinct Improvement in Hb and WBC Levels for Periods of A = 3 Mos, C = 1 Yr B = 6 Mos, C = 1 Yr	Partial	Complete	General Condition of Patient as of March 15, 1941	Date of Death	Hours Between Death and Autopsy	Gross Findings (Weights in Grams)	Microscopical Findings	Peripheral Blood Tissue Excretions	Number
					Hb (%) Sahli	WBC/Cu Mm in Thous										
1	2*	3		20	21	22	23	24	25	26	27	28	29	30	31	31
51 Ande	F 4	1/27/41	LN-D S-D L-U		87 to 66	1750 to 4100				Type 14 Pneumonia 2/28/41	3	Left lung—295 Rt lung—150 Liver—1100, spleen—80 Consolidation of left lung		T	51	
52 Andr	F 1½	9/11/40	LN-U S-U L-U							9/17/40	6	Typical findings	Marrow—typ leukemic hyperplasia Liver—fatty degeneration Kidneys—marked infiltration Nodes and spleen—leuk infiltration	T	52	
53 Bel	M 37	7/15/39	LN-I S-I L-U		21 to 64	21 to 125				9/ 1/39	6	Liver—2350, spleen—800, kidneys—firm	Lymphoid infiltration of most organs, including marrow, kidneys and submucosa of G I tract	T	53	
54 Bor	M 2	1/ 5/39	LN-I S-U L-D		25 to 70	4 to 20				7/22/39	4	Liver—560, spleen—100	Lymphoid infiltration of most organs, including marrow, kidneys, and submucosa of G I tract		54	
55 Brn	F 8	12/10/40	LN-U S-U L-U		Un-changed	Un-changed				1/ 3/41	6	Typical findings	Lymphoid infiltration of many tissues (bone, G I tract, kidneys, marrow spleen)	P B E T	55	
56 Cre	F 3	11/25/40	LN-D (Normal) S-D (Not palp) L-D (Not palp)		100	5000		2 mo	Excellent							56
57 Cie	M 8	11/23/40	LN-U S-U L-U		80	6	2 mo			2/25/41						57
58 Gre	M 45	4/17/40	LN-U S-U L-U		32 to 50	8 to 28				5/19/40	6	Hepato-splenomegaly and lymphadenopathy Marrow red		T	58	

Acute

TABLE III (Continued)

59 Her	M 4	7/12/40	LN-U S-U L-U	28 to 35	1 to 15					7/21/10		PB T
60 Kln	M 9	5/16/38	LN-D S-D (1 cm) L-D (1 cm)	36 to 80	1 to 116					6/12/38		
61 Iud	M 23	12/19/10	LN-U S-U L-U							12/28/10		
62 Rog	F 58	9/ 6/40	LN-U S-U L-U	No change	No change					9/17/10	7	Marrow—hyperplastic (lymphoid infiltration) kidneys and GI tract markedly infiltrated
63 Rog	F 52	3/ 2/40	LN-U S-D (2 cm) L-D (1 cm) (ascites disappear)	28 to 45	2 to 110					5/27/10		
* K 64 Smt	F 24											
65 Tui	F 27	7/23/40	LN-U S-U L-U	23 to 66	1 to 104					2/26/38	18	Spleen—300, liver—1800 All nodes and marrow uni- formly gray
66 Vcl	M 30	6/ 6/40	LN-I S-I L-I	20 to 33	100 to 119					9/11/40		
										7/ 5/40	9	Spleen—900, liver—1850 Both peripheral and cen- tral nodes markedly en- larged
67 Abn	M 73	8/19/40	LN-U S-U L-U	20 to 35	75 to 426					11/28/40	6	Typical leukemic infiltration
68 Bern	M 51	9/23/40	LN-U S-U L-U	No change	No change					9/29/40	6	Broncho-pneumonia Early fibrosis of liver Myocardial sclerosis and degeneration Pul edema
69 Cl	M 73	8/ 2/39	LN-U S-U L-U	64 to 79	19 to 23					9/30/39	-	Spleen—2200 liver—1800 Pancreas unusually hard Marrow pale and watery
70 Chi	M 69	1/13/40	LN-U S-U L-U	60 to 77	6 to 131					5/29/40	7 days	Lymphocytic infiltration of marrow, GI tract, kidneys spleen, pancreas
71 Dry	M 55	5/11/40	LN-D S-D L-D	94 to 114	20 to 195	B			Excel- lent			

Acute

1

1

Chronic

TABLE III (Continued)
Clinical Data After Administration of Radio-Phosphorus

Name and Number	Sex and Age in Years	Date of Admission	Physical and Lab Findings			Remissions			General Condition of Patient as of March 15, 1941	Date of Death	Hours Between Death and Autopsy	Gross Findings (Weights in Grams)	Microscopical Findings	Radio-Phosphorus Studies
			Refers to Change in Size After Administration	LN = Lymph Node S = Spleen L = Liver	Min and Max Levels		Partial	Complete						
					Hb (%) Sahli	WBC/Cu Min in Thous								
1	2	3	20	21	22	23	24	25	26	27	28	29	30	31
72 Foo	M 50	8/30/40	LN-D (15 cm) S-D (1 cm) L-D (1 cm)	54 to 65	51 to 95			Good						72
73 Gm	F 70	4/16/40	LN-U S-U L-U	49 to 61	1000 to 1000				6/22/40				P B	73
74 Gr	F 47	4/23/40	LN-D S-U L-U	78 to 104	27 to 117	B		Excellent					P B _E	74
75 Hrt	M 72	2/20/40	LN-L S-L L-U	62 to 97	18 to 120	C		Good					P B	75
76 Hlog	M 66	7/ 6/39	LN-D (1 cm) S-D (3 cm) L-L	47 to 109	8 to 223	C		Good						76
77 Let	F 61	11/ 8/40	LN-U S-D (8 cm) L-D (6 cm)	58 to 62	441 to 229				12/24/40	9	Spleen—900, liver—2500 Mesenteric nodes were massive Broncho-pneumonia	Typical gen lymphocytic infiltration	P B _T	77
78 Lxt	M 59	3/18/40	LN-L S-L L-U	96 to 107	19 to 74			Excellent					P B	78
79 Mhl	F 61	9/30/40	LN-L S-L L-L	23 to 44	70 to 376				12/27/40					79

Chronic

TABLE III (Continued)

[illegible]

In the study of the patients treated with radio-phosphorus, standardized technic for diagnosis was used. All blood used for cell counts was obtained from puncture wounds of the lobe of the ear. Sahli and Sahli-Osgood hemoglobinometers, and standardized blood cell pipettes were used. Most of the differential cell counts of the blood and of the bone marrow fluid, obtained by sternal puncture, were made by use of the supra-vital technic as well as by the usual Wright Giemsa staining technic. The blood (the amount of which depended on the white cell count, but usually varied from 15 to 50 c.c.) used for radioactivity assays was withdrawn from veins, heparinized, immediately cooled and centrifuged in cold centrifuge cups for 20 minutes at 3000 revolutions, or 1450 times gravity (International Centrifuge, Size 2). First, the buffy coat was removed with a 10 c.c. syringe and a 4-inch 18-gauge needle, the bevelled point of which had been ground off. By gently loosening and aspirating one edge of the buffy coat under good light, the entire coat (which has internal tenacity) along with considerable plasma can be removed from the initial site of aspiration without disturbing the layer of red blood cells or leaving a suspension of cells in the plasma. After the buffy coat, or white cell layer, had been removed, the plasma layer was aspirated off. Equal quantities of isotonic Ringer's solution were then added to both of the suspensions of red blood cells and white blood cells. Both the white and the red cells were gently shaken to wash off the clinging plasma and then the suspensions were centrifuged exactly 20 minutes at 1,450 times gravity so that constant volumes were obtained. Accurate volumetric readings of these packed cells were possible.

Fractions of blood, and aliquot portions of feces and urine were placed in appropriate crucibles and ashed (at 400° C). The radioactivity of each ash was measured by means of DuBridge electrometers, Lauritsen type electroscopes or Geiger counters, each of which was standardized by a uranium standard which is known to emit 500 beta-particles per second. The figures representing the radioactivities were corrected for the rate of decay of radio-phosphorus as indicated on the accompanying tables and graphs.

RESULTS *

A Introductory Remarks on Absorption and Excretion of Radio-Phosphorus

The absorption of orally administered radio-phosphorus from the contents of the gastrointestinal tract depends upon numerous factors,³⁷ among which the important ones are the speed of the phosphorylating mechanism within the gastrointestinal tract and within the body tissues themselves, the metabolic rate, the blood volume, the diet, the age and weight of the patient,

* It must be pointed out again that all the cases on whom absorption and excretion studies were made received "therapeutic" and not "tracer" doses of radio-phosphorus. Therefore exact conclusions concerning the metabolism of phosphorus in leukemia cannot be drawn. Similarly, the doses of phosphorus used in the normal cases may well have produced irradiation effects. However, no changes of the levels of the white blood cells or other evidences of such irradiation effects were observed in the normal individuals.

the intake of P^{31} present in the diet, the amount of sodium phosphate ingested in which the radio-phosphorus is incorporated, the rate of the fecal flow and the vascularity of the gastrointestinal tract, the rates of phosphorus metabolism and the functional capacity of each organ and tissue. Not all of these factors are involved when P^{32} is administered intravenously. Obviously the disease processes to be studied and their effects upon the organs of the body are additional complicating factors. In order to study accurately the phosphorus metabolism of the body, all the factors mentioned and many more would have to be controlled or measured. The effect of one of these factors on absorption was noted. In table 7 (Case 34) it is observed that when large amounts of non-radioactive phosphorus accompany radio-phosphorus, regardless of the method of administration, less of the radio-phosphorus is retained by the blood fractions. This indicates that the varying intake of P^{31} in the average diet will have some effect on the rate of the absorption of administered radio-phosphorus.

The average normal adult person has about 5,000 c c of circulating blood, the proportions of which are roughly as follows: 2,250 c c red blood cells, 50 c c white blood cells, and 2,700 c c plasma. Patients with leukemia may have fewer than 50 c c or as much as 3,000 c c of circulating white blood cells, or they may have fewer than 1,000 c c of circulating red blood cells but they rarely have more than 2,500 c c. Therefore, it must be pointed out that the results have been illustrated on figure 1 as per cent of the dose of radio-phosphorus administered per 100 c c of plasma, whole blood, packed red blood cells, or packed white blood cells. It must be emphasized that figure 1 and figure 2 illustrate only trends. The data for drawing the curves were obtained from tables 7, 8 and 9. Obviously, there are many variations, such as differences in the weights of the patients, differences in the amounts of P^{32} and P^{31} administered, differences in the volumes of the circulating blood elements, differences in the metabolic rates of the blood elements, and others for which corrections were not made.

The rate of excretion of radio-phosphorus in the urine and feces depends upon all the factors mentioned previously and particularly upon the route of administration of P^{32} . The rate of flow of the fecal stream, the total amount of P^{31} and the absorptive capacities and the vascularity of the intestinal mucosa, are among the factors influencing the rate of excretion in the feces when P^{32} is administered orally. When administered orally, P^{32} may or may not be absorbed, if absorbed, may or may not be excreted by the kidneys, or may or may not be excreted by the bowel. When administered intravenously P^{32} can only reach the feces by way of the biliary system or by direct excretion through the gastrointestinal mucosa. (One nervous patient, case 71, who had received intravenously 2.16 Mc of P^{32} , vomited four hours after the administration, and 0.06 per cent of the dose was found in 40 c c of vomitus.) The rate of excretion of P^{32} in the urine depends upon the amount of P^{32} available in the plasma and upon kidney function. The results have been illustrated in figure 2 as percentage of the dose administered.

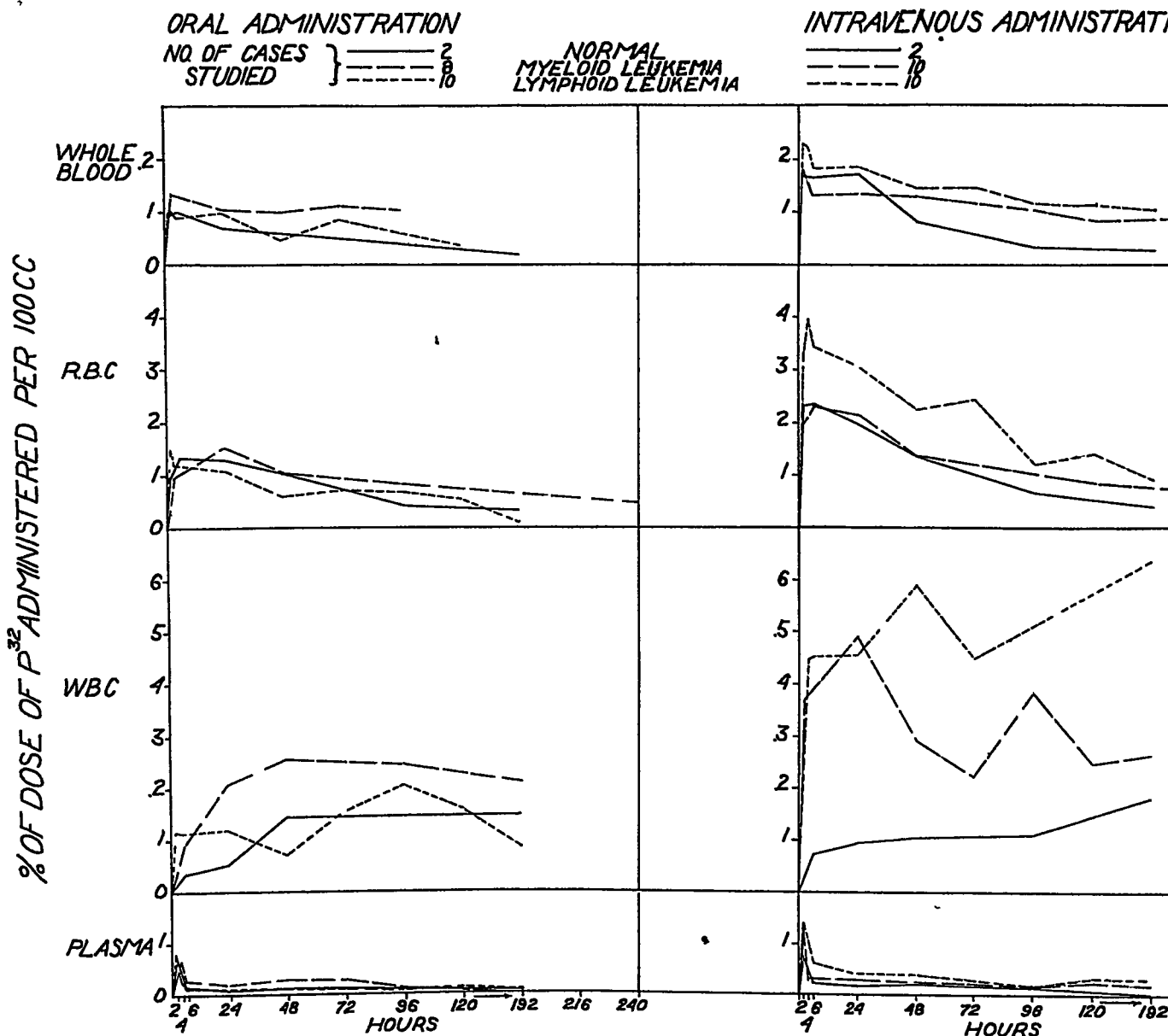


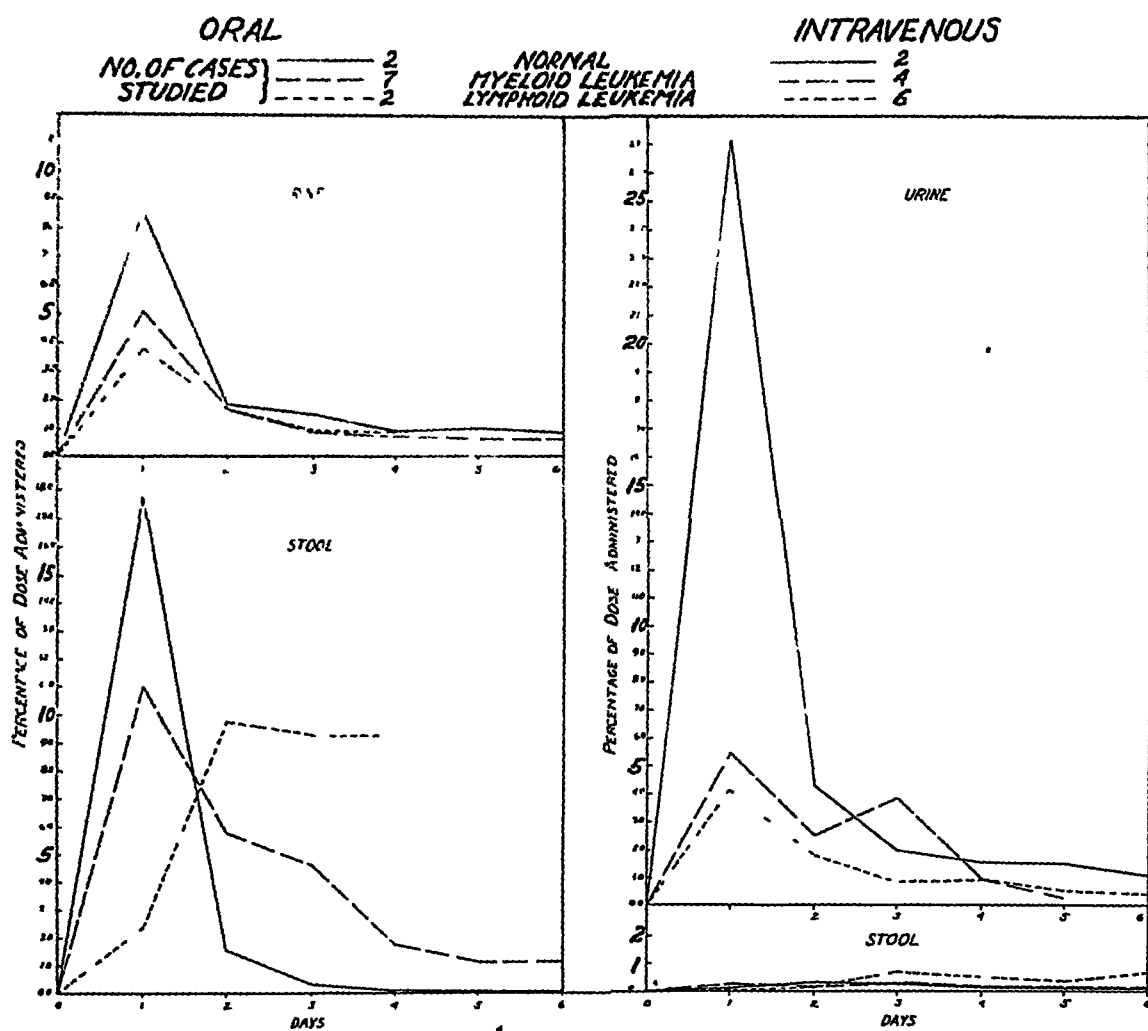
FIG 1 Average retention, in blood fractions, of P^{32} administered orally and intravenously in normal individuals and in patients with leukemia

B Oral Administration of Radio-Phosphorus

1 Absorption (tables 7 and 8 and figure 1, left side)

The rate of absorption of radioactive phosphorus administered orally has been measured in two normal persons and in 18 patients (2 acute and 16 chronic cases). The content of radio-phosphorus in the plasma of all the patients and of the normal persons was greatest before the second hour after administration. After the twenty-fourth hour, lower levels were observed which gradually tapered off to the near zero level on the eighth day.

The maximum level of radio-phosphorus in the red blood cells usually occurred between the sixth and twenty-fourth hours after administration. No correlation could be established between the concentration of radio-phosphorus and the degree of anemia or the amount of hemoglobin.

FIG 2 Average excretion of P^{32} in urine and feces

In the majority of cases, regardless of the chronicity or acuteness of the leukemic process, the P^{32} levels of the white blood cells rose during the first 48 hours and then either continued to rise slowly or maintained a high plateau for days. The content of radio-phosphorus in the white blood cells of normal persons was considerably lower during the first 48 hours than that of leukemic patients, i.e. normal white blood cells retain less radio-phosphorus than leukemic cells. This may be due, among other reasons, to a more rapid rate of phosphorus metabolism, or a more rapid rate of reproduction of the leukemic cells. Unfortunately, the metabolic rates of the leukemic cells were not determined.¹⁵

In case 97 it was possible to measure the amount of radio-phosphorus retained by the platelets. Twenty-four hours after administration, the platelets retained the same amount of radio-phosphorus per unit volume as did the red blood cells.

1

TABLE VII (Continued)									
Plasma									
Whole blood									
R B C									
W B C									
Plasma									
Whole blood									
R B C									
W B C									
Plasma									
Whole blood									
R B C									
W B C									
Plasma									
Whole blood									
R B C									
W B C									
Plasma									
Whole blood									
R B C									
W B C									
Plasma									
Whole blood									
R B C									
W B C									
Plasma									
Whole blood									
R B C									
W B C									
Plasma									
Whole blood									
R B C									
W B C									
Plasma									
Whole blood									
R B C									
W B C									
Plasma									
Whole blood									
R B C									
W B C									
Plasma									
Whole blood									
R B C									
W B C									
Plasma									
Whole blood									
R B C									
W B C									
Plasma									
Whole blood									
R B C									
W B C									
Plasma									
Whole blood									
R B C									
W B C									
Plasma									
Whole blood									
R B C									
W B C									
Plasma									
Whole blood									
R B C									
W B C									
Plasma									
Whole blood									
R B C									

TABLE VII (Continued)

[illegible]

TABLE VIII
Rates of Absorption (Retention) of Radio-Phosphorus in Blood

[illegible]

I Normal Individuals

Whole blood	0091	0606			0102	068	0071	0473	008	04				0037	0246	0015	010	8	600	1500	Mie 1
R B C	0090	0533			0131	0873	0137	0913	0097	0647				0048	032	0041	0273				
W B C	0087	0580			0013	0086	001	0266	0050	0332				0104	0693	009	06				
Plasma	0092	0613			0024	016	0016	0106	0017	0113				0015	010	0005	0033				
Whole blood	0192	1280			0206	1373	0150	10	0128	0853				0089	0593	0045	030	8	600	1500	Rob 3
R B C	0215	1133			0263	1753	0249	166	0170	1133				008	0533	0049	0326				
W B C	0101	0693			009	06	0131	0873	0369	246				0319	2126	034	227				
Plasma	0123	0820			0039	026	0032	0215	0032	0215				0032	0215	0019	0126				

III Lymphoid Leukemia

[illegible]

TABLE VIII (Continued)

Plasma						0118	0236				0165	0099	0198				0081	016	5	300	5000	End 82
Whole blood				0267	0535			0251	0503	0232					0208	0116						
R B C				0553	111	0484	097								0316	069				750	5000	Abne 67
W B C				0646	0128	0119	084								0461	172						
Plasma				009	008	007	004			007	001				006	002						
Whole blood	0225	079	0267	087	087	023	075															
R B C	0175	057	0303	095	043	0372	122										0151	051	9	10000	1050	Hit 75
W B C	0313	102	0132	043	087	0202	066										011	131				
Plasma	0183	06	0118	038	026	0083	027										0055	018				
Whole blood																						
R B C			0482	161								0345	115				020	066	5	150	1000	Lyt 78
W B C			0516	172								0575	192				019	160				
Plasma			0270	090								0099	033				006	02				
Whole blood																						
R B C	0113	037	0175	058		0280	093								0115	038	0081	025	7	3000	3000	Rog (Acute Leukemia) 63
W B C	0184	061	0221	073	076	0292	097								0336	112	0288	095				
Plasma	0127	042	0088	029	025	0035	011								0032	010	0018	003				
Whole blood																						
R B C					076	026	079										0065	019	8	1500	3300	Syp 81
W B C				0250	079	031	097										0330	10				
Plasma				0066	020	0024	007										0021	006				
Whole blood																						
R B C						116	010					074	0061				040	0034	8	1180	11680	T-ly 87
W B C						062	0053					163	011				182	0156				
Plasma						0166	0014					014	0012				008	0007				
Whole blood																						
R B C																						
W B C				017	0697	0155	0635			0148	0607	014	0374									
Plasma				010	041	0145	0594			0178	0730	016	0656									
Whole blood				003	0123	0015	0062			0015	0062	0015	0062									
R B C																						
W B C																						
Plasma																						

Activities corrected for decay and to date of administration

TABLE VIII (Continued)

Periods after Intravenous Administration of P ₂₅																								
Name and Number of Patients Receiving P ₂₅ Both Orally and Intravenously	Interval in Days Between Oral and Intravenous Administrations, or I V and I V Adminis	Name and No of Pts Receiving P ₂₅ Intravenously	Micro-curies of P ₂₅ Administered Intravenously	Milligrams of Sodium Phosphate in Which P ₂₅ Was Incorporated	2 Hours		4 Hours		6 Hours		24 Hours		48 Hours		72 Hours		96 Hours		Other		Time (Days) for Values Under "Other"			
					Total	%	Total	%	Total	%	Total	%	Total	%	Total	%	Total	%	Total	%				
I Normal Individuals																								
Whole blood			1500	600	0251	1673			0249	1660	0350	233	012	080			0058	0386	0037	024	8			
					0336	224			0349	2326	0315	210	0198	132			0091	0606	0047	0313				
					0401	2673			0114	076	0171	114	016	107			0170	1133	0340	227				
					0096	064			0038	0253	0023	0153	003	0207			0019	0126	0009	0060				
Whole blood			1500	600	0260	1733			0257	1713	0168	112					0033	022	0042	028	8			
					0340	2266			0352	2346	0283	1886					0117	078	0071	047				
					0274	1822			0110	0733	0113	0753					0168	112	020	133				
					0131	0873			0028	0186	0036	024					0026	0173	0013	008				
III Lymphoid Leukemia																								
Whole blood	Dr 71	10	1360	150						0208	15		018	13	0132	09								
									0328	24		0183	13	012	08									
									0785	59		0546	43	0590	46									
									008	06		0067	04	0048	02									
Whole blood	Gr 71	6	540	150	0145	26	0143	26	0118	21	045	21					0096	17						
					0220	40	0245	50	0250	46	0234	43					0148	27						
					0188	34	0328	60	0214	39	0165	30					022	40						
					0076	14	0055	10	0041	07	0022	04					0011	02						
Whole blood	Std 82	11	5000	450									0413	0826			0342	068						
																		0544	011					
																		1321	264					

TABLE VIII (Continued)

[illegible]

Total amounts expressed in microcuries per c c , percentages in % of dose per 100 c c

The Ringer's solution which was used as a wash for the blood cells (both white and red) contained usually less than 1 to rarely 10 per cent of the radio-phosphorus in the blood elements—an indication that the amount adsorbed on the surface of the cells or lost through handling, was minimal

2 Excretion (table 9 and figure 2, left side)

The normal individuals excreted in urine and feces a greater percentage of administered radio-phosphorus than did the patients. And after the forty-eighth hour more P^{32} was excreted in the urine than feces of the normal individuals and there is no reason to assume that this does not continue until all of the P^{32} absorbed by the body is ultimately and eventually excreted. The patients apparently excreted P^{32} more slowly—at least the average rate of excretion of the patients was slower than that of the normal individuals.

As would be expected, a greater quantity of P^{32} was excreted in the feces than in the urine. The P^{32} in the feces was made up of that not absorbed by the gastrointestinal tract and that which was excreted after absorption.

The total percentage of P^{32} excreted in the urine and feces of the normal individuals during the six days following its oral administration varied from 22.9 to 46.3 per cent of the dose administered, of the myeloid leukemia patients during four to six days after administration 14.1 to 45.5 per cent, and of the lymphoid leukemic patients 37.8 to 53.9 per cent.

C Intravenous Administration of Radio-Phosphorus

1 Absorption (tables 7 and 8 and figure 1, right side)

The absorption rates following intravenous administration of radioactive phosphorus to 2 normal individuals and 16 patients (2 acute and 14 chronic cases) were not identical with those noted following oral administration. The levels of radio-phosphorus in the plasma during the first few hours after intravenous administration were slightly higher and the content of radio-phosphorus in the peripheral red blood cells rose more rapidly to considerably higher levels. As can be observed, the leukemic white blood cells took up more quickly and retained greater amounts of P^{32} than did the normal white blood cells. The white blood cells of the normal individuals retained only slightly greater amounts of P^{32} , when it was administered intravenously than when orally, while the leukemic cells retained considerably greater amounts following the intravenous administration.

2 Excretion (table 9 and figure 2, right side)

Small and nearly equal amounts of P^{32} were excreted in the feces of both normal individuals and patients. But the former group excreted more P^{32} in the urine during the first 48 hours than was excreted by the latter group during the same period. The normal individuals excreted more P^{32} in the urine following its intravenous than its oral administration, but this was not true for the patients.

After the period of 48 hours following administration, both groups excreted in the urine and feces similar amounts of P^{32} and this undoubtedly continued until all of the P^{32} absorbed by the cases was ultimately excreted.

During the six days following the intravenous administration of P^{32} the normal individuals excreted from 26.1 to 50.5 per cent of the dose administered, during the four to six days the patients with myeloid leukemia excreted from 5.6 to 24.5 per cent, those with lymphoid, 2.79 to 16.5 per cent.

In summary, therefore, the normal individuals excreted during the period studied about the same amount of P^{32} regardless of route of administration, while the patients excreted, during a similar period, much less when P^{32} was administered intravenously than when orally. The rate of excretion differed in the two groups. Regardless of the route of administration the normal persons excreted P^{32} much more rapidly in the urine and feces than did the patients during the first 48 hours after administration. After that interval, the rates were similar in both groups. In most instances, following the 48-hour period, more P^{32} (quantitatively) was excreted in the urine than in the feces in both groups.

D. Introductory Remarks on Clinical Results

Since the clinical application of artificially produced radioactive agents is still in the experimental stage the majority of patients treated with radio-phosphorus were those who had previously received x-radiation and Fowler's solution. Many of them were in the terminal stages of their disease processes. Until sufficient knowledge of diffuse neoplastic or near-neoplastic diseases has been gained so that their prevention is possible, radiations of various types seem to be the best therapy available for alleviating the symptoms which result. As is well known, some patients with leukemia respond favorably to x-radiation and others do not, similarly, as seen from the experiences related in this report, some respond favorably to the beta-rays of radio-phosphorus while others do not. Radiations which produce sufficient ionization can kill cells. Among other factors, effective therapeutic ionization depends upon the intensity and energy of the radiation in question, the penetrability of the radiation (which depends upon the density of the object irradiated), the constancy of duration of the radiation, and the position or localization of the ionization produced by the radiation.

Among the many types of x-radiation therapy used for leukemia there are (1) the technic in which 100,000 to 400,000 volt roentgen-rays are directed toward the spleen, the peripheral nodes or the long bones, the single dose varying between 50 to 200 r, (2) the Heublein⁴ technic, which consists of the use of small amounts of high voltage (150 to 200 k v) x-radiation over prolonged periods (7 to 21 days) to the whole body at long distances (15 to 20 feet), the total dose varying between 200 to 400 r during a 2-week period (average of about 20 r per 24 hours), and (3) the "spray"²⁸ technic, which consists of the use of high voltage x-radiation directed towards the whole body (alternately front and back) at 50 to 100 cm distance, the total dose varying between 50 to 60 r which is given in a few minutes of time. Unlike roentgen-rays, which penetrate many centimeters of water, the beta-

TABLE IX
Rates of Excretion of Radio-Phosphorus in Urine and Feces

Periods after Oral Administration of P ₃₂													Micro-cures of Admin-istered Orally	Milligrams of Sodium Phosphate in Which P ₃₂ Incorporated	Name and Number of Patients Receiving Radio-phosphorus Orally		
1 Day		2 Days		3 Days		4 Days		5 Days		6 Days		Total Excretion					
Total	%	Total	%	Total	%	Total	%	Total	%	Total	%	Total 4-6 Days				%	
I Normal Individuals																	
Urine	60.5	1.63	25.5	1.7	13.4	89	10.9	72	11.1	74	6.75	45	344	22.9	600	Mie	1
Stool	191	12.93	7.8	52	3.32	22	41	02			95	06					
Urine	191.19	12.7	29.5	1.96	31.8	2.12	17.34	1.15	21.22	1.41	16.9	1.12	695	46.3	600	Rob	3
Stool	338.98	22.59	38.8	2.59	5.85	39	3.05	10	14	01	18	01					
II Myeloid Leukemia																	
Urine	275	7.15	56.8	1.47	37.1	96.4	29.0	75.4					545	14.1	930	Beac	14
Stool			82	2.13	56	1.45	9.2	239									
Urine	730.8	5.4	236.8	1.8	201.6	1.6	189	1.5	176.4	1.4	176.4	1.4	2898	23.0	20		
Stool	911.2	6.7	189	1.5	126	1.0	25.2	2			12.6	1					
Urine	255	6.17	63	1.57	41.8	1.45	24.5	61					831	20.8	1000	Cole	17
Stool	17	01	270	6.75	158	3.97	18.7	46									
Urine	163.9	3.49	35.76	76	29.8	635	28.62	571	26.82	571	26.82	571	814	17.3	3000	Ebey	19
Stool	238.1	5.18	50.6	1.27	53.64	1.14	50.66	1.08	50.66	1.08	50.66	1.08					

TABLE IX (Continued)

Urine	35 76	6	17 88	3	11 92	2	11 92	2	25 96	1	1 488	25 1	2800	5960	Hay 97
Stool			911 9	15 3			447								
Urine	564	12	239 7	5 1	42 93	9	38 16	8	32 39	7	2134	15 4	3000	4700	Ken 27
Stool	987	21	164 5	3 5			23 85	5		2					
Urine	19 08	4	47 7	1	28 62	6	23 85	5	19 08	1	1712	35 9		1700	Welc (Ac Leuk.)
Stool	858 6	18			572 4	12	33 39	7		1 9					

III Lymphoid Leukemia

Urine	12 3	3	64 5	1 61	59 5	1 48	37 6	94																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																														
-------	------	---	------	------	------	------	------	----	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--

Activities corrected for decay and to date of administration

TABLE IX (Continued)

Time and Number of Patients Receiving Orally and Intravenously		Interval Between Oral and Intravenous Administrations	Time and Number of Patients Receiving Radio-Phosphorus Intravenously	Micro-curies of P_{32} Administered Intravenously	Milli-grms of Sodium Phosphate in Which P_{32} Was Incorporated	Periods after Intravenous Administration of P_{32}																			
						15 Min		2 Hours		4 Hours		1 Day		2 Days		3 Days		4 Days		5 Days		6 Days		Total Excretion	
						Total	%	Total	%	Total	%	Total	%	Total	%	Total	%	Total	%	Total	%	Total	%	Total 4-6 Days	%
I Normal Individuals																									
Urine			Per	1500	600						565 2	37 66	75 5	5 03	37 3	2 48	25 41	1 69	26 16	1 74	17 49	1 16	760	50 5	
Stool			2								1 47	098	3 87	25	3 72	24	2 49	16	35	02	77	05			
Urine			Vic	1500	600						250	16 66	52 5	3 5	22 6	1 5	22 2	1 48	19 11	1 27	16	1 06	391	26 1	
Stool			4								1 29	08	5 74	45					30	02	15	01			
II Myeloid Leukemia																									
Urine	Rece	7		870	150						27 9	3 21	8 65	99	6 6	75	5	57					49	5 61	
Stool	St												51	05							30	03			
Urine	Ther	210		1110	150		8 5	74	21 5	1 88	10 6	92				1 6	14 4	1 2	2 7	23			85	7 5	
Stool	St										3 62	31	2 26	19	1 37	12	1 12	09							
Urine			Klin	1950	300	25 2					310	16 05	64 2	3 29	45 0	2 39	33 8	1 93					478	24 5	
Stool	St		25																						
Urine			Park	1260	150						11 2	88	63 5	5 03	125	9 91	2 36	18					214	16 9	
Stool	St		39								2 5	19	1 09	08	5 5	43	2 58	20							

TABLE IX (Continued)

[illegible]

III Lymphoid Leukemia

[illegible]

Total amounts and percentages of doses expressed in microcuries

rays emitted by radio-phosphorus penetrate less than 1 cm of water, but both cause ionization in body tissues. However, the radio-phosphorus atom localizes in the body cells themselves and may remain there for prolonged periods. Therefore x-radiation given by technic (2) is more comparable to the beta radiation of P^{32} than technics (1) and (3).

E Clinical Results

The clinical results are recorded in tables 1 to 6. A summary of the results of the two large groups of patients (tables 2 and 3) follows.

Type of Disease	Myeloid Leukemia		Lymphoid Leukemia	
	Acute	Chronic	Acute	Chronic
No of cases	8	38	16	25
No of partial remissions	0	11	1	8
No of complete remissions	0	5	1	1
No dead	8	21	15	13

The duration of the partial and complete remissions and the various time intervals involved are indicated on the tables. Two patients (cases 27 and 30) have had essentially complete remissions for nearly two years. We have failed to find other examples in the literature of authentic cases of leukemia with complete remissions of two years' duration. As is well known, both complete and partial remissions may occur spontaneously and many remissions of a rather prolonged nature have been reported following transfusions, infections and the administration of various specific agents (H W Jones, F R Miller and W A Hause, Trans Assoc Am Phys, 1940, 4, 54) or less specific ones such as adenylic acid and nucleotides. One of us (L A E) has observed temporary but complete remissions in 3 patients with leukemia following transfusion of blood of donors who were suffering with symptoms of mild influenza. It is unfortunate that the percentages of partial and complete remissions of all cases of leukemia recorded in the literature are not known.

Of 10 patients with chronic lymphoid and 12 with chronic myeloid leukemia who had had no therapy previous to that of radio-phosphorus, 4 in each group died (3 in the former group and 1 in the latter were moribund when P^{32} was first administered) while the other 14 had either partial or complete remissions of six months to a year in duration. The results in those patients who had had x-radiation previously to the administration of radio-phosphorus are not so encouraging, and it is from this experience that we feel that x-radiation reduces the effectiveness of radio-phosphorus since the duration of the disease processes previous to administration of radio-phosphorus was quite similar in both groups just mentioned.

Although the physical and symptomatic changes are indicated on the tables (1 to 4) all of the hematological changes cannot be. Therefore table 10 lists in some detail the blood findings of 10 patients with lymphoid

and 10 with myeloid leukemia and one with a leukemoid reaction which are among those with interesting changes (Two of the cases (numbers 56 and 88) with lymphoid leukemia, listed in table 10, and case 43 with myeloid leukemia, table 2, were given neutron radiation, produced by the deuteron beam of the cyclotron directed against beryllium. The hematological responses were satisfactory. This opens a new field for the investigation of the clinical response of patients with leukemia to whole body irradiation with neutrons.) By examining the results recorded on table 10 one can observe that in many instances the white blood cell levels decreased, the differential

TABLE X
Blood Levels Following Administration of Radio-Phosphorus

Case No	Name Sex Age	Inclusive Dates of Administration	Amount (Mc) and Route of Ex or Neutron Therapy Admin	Dates of Blood Counts	Hb per cent (Sahl)	RBC in 10 Thousands	WBC in Thousands	Pl in Thousands	Differential									
									Seg Polys	Non-Seg Polys	Myelocytes	Myeloblasts	Lymphocytes	Lymphoblasts	Monocytes	Others		
A Myeloid Leukemia																		
14	Beac M 45	5/22/40 to 9/25/40	87 (I V) 14 J1 (O)	5/ 6/40 7/19/40 11/12/40 2/10/41	59 93 96 110	296 469 507 628	164 80 11 10	200 600 260 700	34 14 62 67	14 38 8 9	46 41 14 —	1 1 — —	3 2 12 21	— — — —	— — — —	— — — —	2 4 2 3	
17	Cole M 23	5/27/40 to 1/ 8/41	19 (O)	5/23/40 1/ 8/41	81 110	405 597	148 38	200 238	40 51	19 10	35 14	4 —	2 2	— —	— —	14 —	— 9	
22	Hall F 49	10/ 7/40 to 12/27/40	16 9 (O)	10/ 7/40 1/28/41 3/ 5/41	67 100 111	275 541 567	380 124 67	414 334 400	10 26 23	36 36 33	46 32 29	2 — —	1 4 7	— — —	— — —	— — —	5 2 7	
27	Kenn M 21	11/29/38 to 6/ 7/39	10 72 (O)	11/ 4/38 5/ 4/39 8/ 1/39 1/ 9/40 2/26/41	86 89 96 100 105	342 462 448 438 510	200 35 12 13 11	720 260 205 150 175	32 41 51 67 52	25 24 9 9 8	29 19 9 — —	1 — — — —	6 11 20 21 22	— — — — —	— — — — —	3 1 7 1 10	4 4 1 1 8	
28	Klin M 31	6/13/40 to 11/23/40	1 95 (I V) 17 (O)	5/13/40 6/24/40 12/16/40	76 88 94	— 510 —	103 67 67	— 253 —	45 60 —	17 18 —	31 17 —	4 — —	— — —	— — —	— — —	— 1 —	3 3 —	
29	Kret M 11	7/14/39 to 2/ 4/41	28 (O)	7/16/39 12/22/39 7/22/40 1/28/41 2/ 4/41 2/16/41	56 74 95 90 68 (Died)	354 365 517 480 410 —	380 6 10 8 6 —	— — — — — —	20 40 43 29 24	17 45 5 35 43	59 4 7 15 22	2 — — 18 9	2 — 38 — —	— — — — —	— — — — —	— 4 — — —	— 1 3 3 1	
30	LaV F 44	1/ 4/39 to 2/17/41	21 72 (O)	6/10/35 12/ 7/38 5/15/39 11/17/39 2/23/40 3/ 4/41	75 99 103 97 100 94	— 402 470 395 458 572	208 30 65 18 6 12	— 448 530 470 335 500	— 41 51 54 41 66	— 11 16 12 11 5	— 21 9 2 2 7	— 1 2 10 31 14	— 14 12 2 — —	— — — — — —	— — — — — —	— 5 4 2 6 6 8	— 7 6 6 9 8	
33	Mars F 11	4/13/40 to 2/19/41	17 17 (O)	4/16/40 7/31/40 2/ 8/41	88 106 100	476 583 515	125 42 27	105 50 100	14 44 50	23 9 6	53 21 23	2 — —	— 13 15	— — —	— — —	— 4 5	8 9 1	
35	Mont M 37	6/27/40 to 1/23/41	32 (O)	6/20/40 1/31/41 3/ 6/41	80 87 98	390 430 512	147 14 9	— 300 —	59 44 44	21 14 5	18 — —	1 — —	— 38 37	— — —	— — —	— 2 3	1 2 11	
37	Nuti M 57	5/ 2/40 to 2/18/41	9 7 (I V) 25 52 (O)	5/ 3/40 3/ 4/41	68 87	354 438	368 74	358 200	20 30	19 37	51 26	3 —	— —	— —	— 2	1 —	6 5	

TABLE X (Continued)

Case No	Name Sex Age	Inclusive Dates of Administration	Amount (Mc) and Route of P ₃₂ or Neutron Therapy Adm	Dates of Blood Counts	Hb per cent (Sahl)	RBC in 10 Thousands	WBC in Thousands	Pl in Thousands	Differential							
									Seg Polys	Non-Seg Polys	Myelocytes	Myeloblasts	Lymphocytes	Lymphoblasts	Monocytes	Others
B Lymphoid Leukemia																
56	Crew F 3	12/18/40 to 1/27/41	45 N	11/25/40 1/ 3/41 1/ 8/41 2/ 7/41 3/12/41	41 49 46 96 96	285 227 210 435 592	3 1 3 5 6	84 22 96 156 130	17 8 42 38 39	1 12 27 13 33	— — — — 5	— — — — —	76 74 29 36 18	2 2 — — —	4 4 2 8 3	— — — 5 3
57	Fier M 8	11/24/40 to 11/29/40	2 0 (I V)	10/24/40 12/13/40 1/29/41 2/25/41	67 57 44 (Died)	380 320 222	40 4 1	10 90 10	1 2 2	— 25 2	— — —	— — —	99 71 87	— — 8	— — —	— 2 1
71	Dryd M 55	5/11/40 to 1/ 2/41	1 36 (I V) 21 2 (0)	5/ 2/40 10/ 7/40 1/23/41 2/13/41	94 114 108 94	535 475 484 481	195 70 35 20	210 — — —	7 6 11 11	5 5 5 4	— — — —	— — — —	88 88 76 78	— — — —	— 1 5 4	— — 3 4
74	Grah F 47	4/29/40 to 1/22/41	4 5 (I V) 22 74 (0)	4/23/40 7/ 1/40 12/ 9/40 2/18/41	97 97 99 97	429 430 463 555	101 47 34 27	214 235 148 133	5 9 2 3	1 4 2 5	— — — —	— — — —	93 86 90 88	— — — —	1 1 5 5	— — 1 2
75	Hatf M 72	2/21/40 to 3/18/41	59 7 (0)	2/20/40 6/24/40 10/ 9/40 2/18/41	97 71 68 61	477 310 423 376	110 33 29 54	150 91 80 —	2 3 4 3	2 3 1 1	— — — —	— — — —	91 95 88 93	3 — — —	2 — 2 —	— — 5 3
76	Hork M 66	8/18/39 to 1/ 3/41	4 8 (I V) 20 12 (0)	7/ 6/39 8/18/39 10/ 9/39 3/27/40 9/13/40 2/25/41	62 50 72 86 99 92	232 220 260 386 401 477	223 51 12 13 9 9	— 22 95 139 278 85	2 2 21 32 37 42	4 1 8 5 4 7	— — — — — —	— — — — — —	94 96 60 52 54 35	— — — — — 15	— 1 8 6 — —	— — 3 5 5 1
80	Mick M 55	2/ 9/39 to 3/ 9/40	59 42 (0)	2/ 3/39 8/18/39 3/ 4/40	68 90 86	326 434 424	115 41 11	90 115 100	3 24 27	3 4 9	— — —	— — —	92 59 61	2 — —	— 4 —	— 9 3
83	Sing M 59	12/31/39 to 8/19/40	33 63 (0)	12/28/39 5/ 1/40 11/19/40 3/11/41	43 62 70 66	250 346 309 315	21 7 10 7	210 103 253 321	21 32 28 22	11 15 19 24	— — — —	— — — —	60 40 47 46	6 — — —	— 8 5 4	2 5 1 4
88	Todd M 45	11/29/40 to 1/31/40	50 N	11/13/40 12/23/40 2/13/41	111 111 110	535 541 558	59 23 21	321 346 —	— 20 35	2 12 24	— — —	— — —	85 61 31	11 6 4	— — 6	2 1 —
91	Youn M 67	4/12/40 to 1/12/41	2 6 (I V) 24 (0)	4/11/40 7/ 1/40 2/19/41	99 80 60	442 414 33	68 21 1	140 160 54	9 2 2	3 6 3	— — —	— — —	86 90 95	— — —	— — —	2 2 —
C Leukemoid Reaction																
97	Heyd M 59	2/26/40 to 3/21/40	15 16 (0)	2/14/40 3/19/40 8/ 6/40 12/ 5/40 3/ 6/41	110 90 100 110 115	525 528 587 — —	55 44 18 14 26	256 — — — —	40 61 77 — 64	40 8 10 — 11	16 25 2 — —	1 — — — —	4 5 8 — 21	— 5 — — —	— — 2 — 4	— — 1 — —

counts improved and the hemoglobin levels rose following the administration of radio-phosphorus

In general, the clinical response of patients with acute types of leukemia to radio-phosphorus is as unsatisfactory as is that following other types of

therapy but in chronic cases the results are as good if not better than those following any other type of therapy

F Autopsy Findings

The radioactivity assays of the tissues obtained at autopsy will be reported elsewhere⁵ The gross findings were typical of those usually described for leukemia The microscopic findings were interesting in that there were no cellular changes in normal cells that could be attributed to local irradiation due to deposition of radio-phosphorus In many sections cellular lysis or rhexis was observed in leukemic cells, however A finding of interest, which is usually not considered seriously in the pathology of leukemia, was the presence of varied degree of infiltration of the mucosa and submucosa of the gastrointestinal tract with leukemic cells in the majority of the patients with lymphoid leukemia,²⁹ and many with myeloid leukemia¹⁴ In cases 84 and 87 the infiltration in the mucosa and submucosa was sufficiently severe to permit perforation of the intestinal wall Mild diverticulitis was present in the latter patient, who died of a *B coli* septicemia The kidneys and adrenals of the cases with myeloid leukemia were seldom infiltrated with leukemic cells while those of cases with lymphoid leukemia were frequently infiltrated Only two of the patients (cases 85 and 99) showed infiltrations in the brain (In fact, only two patients—cases 70 and 82—complained of neurological symptoms)

The conclusion may be drawn that the amounts of radio-phosphorus so far administered have not morphologically altered normal tissues

DISCUSSION

Leukemia is a fatal disease characterized clinically and pathologically by various well-known alterations of the hematopoietic system¹⁰ It varies from a truly malignant, irreversible invasive process to a rather mild cellular infiltrative process in which complete hematological and clinical remissions may occur for periods of 6 to 12 months* The more acute types of leukemia occur frequently in children, presumably because it is generally accepted that children have more growth promoting substances The pathological states classified under the term "leukemia" probably are of as many types and have as many causes as the pathological states listed under the term "infection" Occasionally leukemoid reactions may be indistinguishable from true leukemia both clinically and hematologically, but these processes are completely reversible when the primary etiological agent is removed

Some of the features other than those associated with radio-phosphorus observed during the course of this study are noteworthy As has been noted in the investigations of others who work in the northern hemisphere, and

* Among the various types of leukemic blood cells, many presumably are mutants with excessive growth capacities In case 63 the lymphoid cells of the peripheral blood had sufficient characteristics of malignant growth to make possible their cultivation on artificial media for indefinite periods of time The patient lived only six months after the onset of the disease In cases 71 and 75 lymphoid leukemic processes have existed 12 and 11 years respectively, and reproduction of their white blood cells on artificial media did not occur

in the majority of the cases of leukemia listed here (63 out of 91), the onset of the clinical symptoms frequently occurs during winter or spring Webster,³⁸ Sabin and Duffy³¹ and Brues² have shown that among other things, inadequate diets lower resistance to disease Rhoads et al³⁰ have shown that inadequate diets predispose dogs to indol-induced anemia Lewisohn et al²³ were able by injections of yeast extract to cause complete regressions in 25 per cent of spontaneous breast adenocarcinomata of mice Sugira, Rhoads, Kensler et al^{38, 16} have produced partial protection in rats against liver cancer caused by butter yellow with riboflavin with casein and with rice bran and yeast extract Lavik and Baumann¹⁷ have increased the incidence of hydrocarbon-induced skin cancer of mice 50 per cent by feeding diets high in various fats and oils J B Mider and J White found that mice painted with methycholanthrene would develop leukemia when fed a diet rich in sulfur containing amino acids, but would develop arteriosclerosis when fed a diet poor in such acids (the paper will appear in the Jr of the Nat Cancer Inst) It is well known that during the winter months the diets consumed by human beings living particularly in the central and northern portions of the northern hemisphere are nutritionally inferior to those consumed during the summer months Human white blood cells reproduce rapidly, the average span of life of white cells is but about four days Nutritional deficiencies which would be of short duration such as those that follow periods of emotional trauma or nervousness would be more apt to effect cellular abnormalities in those cells frequently undergoing mitosis than in those that do not reproduce rapidly Ussing³⁶ has shown that in rats 10 per cent of liver protein and about 2.5 per cent of muscle protein are newly formed from the food absorbed in the course of three days of feeding Marshak²⁶ has shown that mouse leukemic cells and presumably regenerating liver cells double in number every 56 hours From these data it is possible to deduct that a factor in the diet or a lack of some factor, could initiate hybrid formation of rapidly developing white blood cells, and that possibly certain foods could prevent or inhibit the initiation of hybrid formation

A Diet

In view of this deduction many of the patients presented here were questioned regarding their diets It was noted that many of them ate what may be considered a poor diet A diet was considered inadequate if it contained only cooked muscle meats, cooked fruits and vegetables, highly processed breads and pastries, and processed or pasteurized milk In other words, no raw foods or living cells were consumed An adequate or "mixed" diet was considered as one that contained daily, among other foods, at least some of the following rare muscle meats, glandular meats (sweetbreads, liver, kidney, tripe, brain, mixed sausages, giblets, etc), raw oysters, strong cheeses containing molds and bacteria (as Roquefort and Camembert), uncontaminated raw milk, coarse breads and raw vegetables and fruits In eliciting the dietary history, all foods consumed were considered

This classification of diets is subject to many criticisms but it is an initial attempt to note dietary differences. Of the eight patients with acute myeloid leukemia, three regularly consumed the "mixed" diet for years previous to the onset of the symptoms of leukemia, four regularly consumed the inadequate diet, and one was not questioned. Of 38 with chronic myeloid leukemia, three consumed the "mixed" diet, 25 the inadequate diet, and 10 were not questioned. Of the 16 with acute lymphoid leukemia, one took a "mixed" diet, three an inadequate diet, and 12 were not questioned. Of the 25 with chronic lymphoid leukemia, three took a "mixed" diet, 20 an inadequate diet, and two were not questioned. The ability of the patients to store various nutrients obviously was impossible to elicit. The enormous numbers of human beings who consume so-called inadequate diets but in whom leukemia does not develop of course would be impossible to determine.

In summary, it has been observed that many patients with leukemia consumed diets previous to the onset of leukemia which were considered inadequate and that in the majority of the patients the symptoms of leukemia developed during the winter months when the diet is most likely to be inadequate for short periods of time, at least. Poor or inadequate nutrition may initiate cellular abnormalities or may lower "resistance" of regenerating cells to various poisonings (benzene,¹¹ benzene ring compounds, carcinogens, etc.) which in turn may lead to the formation of abnormal cellular hybrids. It is known that once an irreversible neoplastic process has been initiated and established, adequate nutrition enhances rather than reverses its growth. If leukemia is such a process initiated by a deficiency, the addition of the deficient agent to the diet would probably not alter the course of an established leukemic process^{3, 27}.

B *Gastrointestinal Tract*

Another feature observed was the occurrence of episodes of diarrhea or attacks of "slimy stools" in a rather high percentage of patients with lymphoid leukemia. It occurred much less frequently in those with myeloid leukemia. The attacks were irregular in duration and intensity but frequently preceded relapse or an acceleration of the leukemic process. Of 25 patients with chronic lymphoid leukemia, 14 had attacks of diarrhea or slimy stools during the course of the disease, six did not, and five were not questioned. Of 16 patients with acute lymphoid leukemia, four had attacks of diarrhea, one had none and 11 were not questioned. Among the 46 patients with acute and chronic myeloid leukemia, only five of the 28 questioned had episodes of diarrhea. As was stated above, the sub-mucosa of the gastrointestinal tract of patients with lymphoid leukemia often becomes variably infiltrated. Since there is some evidence that the majority of the lymphocytes may be produced in the submucosa of the gastrointestinal tract,⁶ the process of lymphoid leukemia may originate by the abnormal production and release of the lymphocytes from this region, and an abnormal excretion of lymphocytes may be responsible for the occurrence of "slimy stools." Of

the four patients (cases 52, 62, 63 and 72) with ascites, due probably to congestion of the lymphatic system of the gastrointestinal tract, all suffered with lymphoid leukemia. It is concluded that the gastrointestinal tract may play a significant rôle in leukemia, particularly lymphoid leukemia.

C *Associated Disease*

Many observers have reported that various diseases or conditions preceded or were associated with leukemia. Similar associated conditions were noted in the group of patients included in this report. In 12 patients (cases 11, 25, 29, 36, 45, 48, 58, 72, 74, 75, 82 and 86) the onset of leukemia was preceded by symptoms of influenza. In eight (cases 5, 19, 22, 28, 30, 43, 71 and 88) the onset was preceded or associated with dental symptoms (toothache, loose teeth, etc.). In two (cases 16 and 36) the disease process was noted near the end of the term of pregnancy.⁷ In six (cases 33, 46, 47, 48, 71 and 90) trauma^{24, 39} (fractures, various accidents) had occurred previous to the onset of symptoms. In 10 (cases 7, 25, 32, 33, 54, 55, 56, 60, 65 and 95) rarefaction of bones was found upon roentgenological examination early in the course of the disease. The work of Iwatsura and Nanjo,¹² who noted particularly a marked increase in phosphatase activity of the serum of patients with myeloid leukemia, offers an explanation for the rarefaction of bones and loose teeth which occur occasionally in the myeloid type of the disease. Increased concentrations of serum-phosphatase may "open" healed calcified tubercles. Five patients (cases 14, 20, 41, 46—myeloid, and 81—lymphoid) had had active tuberculosis¹³ but the pulmonary tubercles had been well walled off as indicated by roentgenological pictures several years preceding the onset of symptoms of leukemia. However, two (cases 41 and 46) of these patients after the onset of myeloid leukemia developed a diffuse density of the lungs and at autopsy diffuse miliary tuberculosis was found. The other three patients are being watched closely. Four patients (cases 24, 31, 63 and 81) were vaccinated during the course of the disease and the reactions were extremely severe. In two of these cases most of the dorsal aspect of the vaccinated arm sloughed off before death and the other two patients developed large necrotic areas which had not healed six months after vaccination.

D *Benzene*

Another possible etiological factor to which increasing weight is being given is the rôle played by compounds which prominently contain the benzene ring.¹¹ Many cases of leukemia following exposure to benzene⁹ and many cases with leukemoid reactions following treatment with substances in which the benzene ring is prominent have been reported in the recent literature. Three patients (cases 58, 74 and 78) of the group herein reported as well as three patients observed more recently, had ingested large amounts of the "sulfone group" of compounds just before the onset of the leukemic processes. One patient, not listed in this report, had a severe myeloid leukemoid reaction (hemoglobin 30 per cent, white blood count 80,000, with 35 per

cent myelocytes) following sulfanilamide therapy from which she recovered after cessation of the therapy. On the other hand, evidence has been presented^{31,32} that clinical and hematological improvement occurs in patients with leukemia following the administration of sulfapyridine. Three patients (cases 10, 46 and 81) had been painters, one (67) had been a printer and in addition took 2 N R tablets daily for 10 years, another (82) took mineral oil daily for 5 to 6 years preceding onset of leukemia. One patient (32) worked for 18 years in a benzol refinery, and another (88) together with a crew associate simultaneously developed chronic lymphoid leukemia after both had worked for a period of 10 years' duration in engine rooms of U S Navy submarines.

E *Sunlight*

A number of patients (cases 42, 54, 69, 71 and 75) apparently experienced symptomatic and even hematological improvement following exposure to sunlight³². The number of circulating white blood cells can be influenced by the rays of the sun, by roentgen-rays, by beta rays, by neutron rays, by ultra-violet rays, etc.

F *Heredity*

Since the influence of heredity on leukemia has been widely discussed, from both clinical and experimental standpoints it is merely mentioned here. Case 38 had a maternal aunt and a cousin (son of the aunt) both of whom died of leukemia. All three had the myeloid type of the disease and in each case the duration of the disease was three years. A maternal aunt of case 7 and the mother of case 88 died of leukemia. The daughter of case 76 has developed splenomegaly at the time of this writing.

In summary, the foregoing discussion indicates that both intrinsic or hereditary and extrinsic or environmental factors may be involved in the etiology of leukemia and suggests, as is well known, that there is some fundamental underlying change responsible for the onset of leukemia which so far is not understood.

CONCLUSIONS

1 The rates of absorption of radio-phosphorus, for four to eight days following "therapeutic" doses administered intravenously and orally, by the plasma, red blood cells and white blood cells of normal individuals and patients with myeloid and lymphoid leukemia, are presented (figure 1). Circulating leukemic cells retain radio-phosphorus in greater concentrations than normal circulating white blood cells.

2 The rates of excretion in urine and feces of radio-phosphorus, administered similarly and to the same groups as described in paragraph 1, are presented (figure 2). Normal individuals excrete radio-phosphorus more rapidly than patients with leukemia during the first 48 hours after administration. The rates after the 48-hour period are similar and proceed undoubtedly until all of the radio-phosphorus absorbed has been excreted.

The total percentages of P^{32} excreted by the groups for a period of 4 to 6 days following the administration of various doses are also presented (table 9)

3 Clinical and hematological results following administration of radio-phosphorus to patients with leukemia are presented (tables 2, 3, 4, 5 and 10) Radio-phosphorus is as effective as other types of treatment in general use, can be easily administered orally or intravenously, produces no nausea, weakness or anorexia following administration, and the results are sufficiently encouraging to warrant intense investigation Two cases of leukemia with essentially complete remissions of nearly two years' duration are reported Both are still alive at this writing

4 In the doses described herein, radio-phosphorus produced no morphological damage to normal tissues

5 Various intrinsic and extrinsic factors which may be associated with leukemia are discussed

We acknowledge with pleasure the courteous cooperation that we have received from the members of the staff of the Crocker Radiation Laboratory, University of California Hospital, Southern Pacific Hospital, Alameda County Hospitals, Children's Hospital of the East Bay, Alta Bates Hospital and others We also wish to acknowledge valuable assistance from members of NYA of the University of California

REFERENCES

- 1 BLUM, L, and COMBS, S Chronic lymphatic leukemia complicated by Type III pneumococcus pneumonia Recovery from pneumonia with sulfapyridine and serum, Jr Indiana State Med Assoc, 1940, 424
- 2 BRUES, D T Food, drink and evolution, Science, 1939, xc, 145
- 3 CASTLE, W B, MEYER, O O, and CHEW, W B Negative results of treatment of chronic myelogenous leukemia as a deficiency disease, Proc Soc Exper Biol and Med, 1935, xxxii, 660
- 4 CRAVER, L F, and MACCOMB, W S Irradiation of entire body, Heublein method, N Y State Jr Med, 1934, xxxiv, 249
- 5 ERF, L A Clinical studies with the aid of radio-phosphorus II The retention of radio-phosphorus by tissues of patients dead of leukemia (to be published in Am Jr Med Sci)
- 6 ERF, L A The disappearance of intravenously injected lymphocytes in the absence of the gastrointestinal tract, Am Jr Med Sci, 1940, cc, 1
- 7 ERF, L A, and FINE, A Serial blood and bone marrow findings of an eighth-month premature and its roentgen-ray treated chronic myeloid leukemic mother, Am Jr Med Sci, 1938, cxcv, 8
- 8 ERF, L A, TUTTLE, L W, and SCOTT, K G The retention of orally administered radio-phosphorus by mice, Proc Soc Exper Biol and Med, 1940, xlv, 652
- 9 ERF, L A, and RHOADS, C P The hematological effects of benzene (benzol) poisoning, Jr Ind Hyg and Tox, 1939, xxi, 421
- 10 FORKNER, C E Leukemia and allied disorders, 1938, Macmillan Co, New York
- 11 HESS, W Respiration and fermentation of tissue in leukemia produced by benzene, Frankfurt Ztschr f Path, 1935, xlvii, 522
- 12 IWATSURA, R, and NANJO, K Phosphatase activity of blood serum and urine in chronic myeloid leukemia, Biochem Ztschr, 1939, ccc, 422
- 13 JAFFE, R H Tuberculosis and leukemia, Am Rev Tuberc., 1933, xxvii, 32
- 14 JOHNS, E I Intestinal ulceration in myelogenous leukemia, Lancet, 1940, i, 174

- 15 KEMPNER, W. The nature of leukemic blood cells as determined by their metabolism, *Jr Clin Invest*, 1939, *xviii*, 291.
- 16 KENSLER, C J, SUGIURA, K, YOUNG, N F, HALTER, C R, and RHOADS, C P Partial protection of rats by riboflavin with casein against liver cancer caused by dimethyl-aminoazobenzene (butter yellow), *Science*, 1941, *xiii*, 308
- 17 LAIK, P S, and BAUMANN, C A Dietary fat and tumor formation, *Cancer Research*, 1941, *i*, 181
- 18 LAWRENCE, E O, and COOKSFY, D On the apparatus for the multiple acceleration of light ions to high speeds, *Phys Rev*, 1936, *i*, 1131
- 19 LAWRENCE, J H, and SCOTT, K G Comparative metabolism of phosphorus in normal and lymphomatous animals, *Proc Soc Exper Biol and Med*, 1939, *xi*, 694
- 20 LAWRENCE, J H, SCOTT, K G, and TUTTLE, L W Studies on leukemia with the aid of radioactive phosphorus, *Internat Clin*, 1939, *iii*, 33
- 21 LAWRENCE, J H, TUTTLE, L W, SCOTT, K G, and CONNOR, C L Studies on neoplasms with the aid of radioactive phosphorus I The total phosphorus metabolism of normal and leukemic mice, *Jr Clin Invest*, 1940, *xix*, 267
- 22 LAWRENCE, J H Nuclear physics and therapy, preliminary report on a new method for the treatment of leukemia and polycythemia, *Radiology*, 1940, *xxv*, 51
- 23 LEWISOHN, R, LEUCHTENBERGER, C, LEUCHTENBERGER, R, and LASZLO, D Effect of intravenous injections of yeast extract on spontaneous breast adenocarcinomas in mice, *Proc Soc Exper Biol and Med*, 1940, *xiii*, 558
- 24 LEWSEN, S C Leukemia following trauma, *Lancet*, 1930, *i*, 288
- 25 LIVINGSTON, K E, and MOORE, R D Reaction of leukemic patients to sulfapyridine administration, *New Eng Jr Med*, 1940, *ccxxiii*, 975
- 26 MARSHAK, A Uptake of radioactive phosphorus by nuclei of liver and tumors, *Science*, 1940, *xii*, 460
- 27 MEYER, O O, MIDDLETON, W S, and THEWLIS, E W Therapeutic failure with certain organic substances in leukemia, *Folia Haemat*, 1935, *liii*, 166
- 28 MURPHY, W P Conservative x-ray treatment in chronic leukemia, *Jr Am Med Assoc*, 1940, *cxi*, 1156
- 29 OTT, A Involvement of the gastrointestinal tract in leukemic and similar diseases of the hematopoietic system, *Virchow's Arch f path Anat*, 1936, *ccxcvii*, 548
- 30 RHOADS, C P, BARKER, W H, and MILLER, D K Increased susceptibility to hemolysis by indol in dogs fed deficient diets, *Jr Exper Med*, 1938, *lxvii*, 299
- 31 SABIN, A B, and DUFFY, C E Nutrition as a factor in the development of constitutional barriers to involvement of the nervous system by certain viruses, *Science*, 1940, *xci*, 552
- 32 STOKER, R Clinical aspects and therapy of lymphatic leukemia, *Munchen med Wchnschr*, 1940, 1047
- 33 SUGIURA, K, and RHOADS, C P Experimental liver cancer in rats and its inhibition by rice-bran extract, yeast and yeast extract, *Cancer Research*, 1941, *i*, 3
- 34 TUTTLE, L W, ERF, L A, and LAWRENCE, J H Studies on neoplasms with the aid of radioactive phosphorus II The phosphorus metabolism of the nucleoprotein, phospholipid and acid soluble fractions of normal and leukemic mice, *Jr Clin Invest*, 1941, *xx*, 57
- 35 TUTTLE, L W, SCOTT, K G, and LAWRENCE, J H Phosphorus metabolism in leukemic blood, *Proc Soc Exper Biol and Med*, 1939, *xli*, 20
- 36 USSING, HANS Use of amino acids containing deuterium to follow protein production in the organism, *Nature*, 1938, *cxlii*, 399
- 37 VERZAR, F Absorption from the intestines, 1936, Longmans, Green & Co
- 38 WEBSTER, L T Heredity in infectious diseases, *Jr Heredity*, 1939, *xxx*, 365
- 39 YAGUDA, A, and ROSENTHAL, N Relation of trauma to leukemia, *Am Jr Clin Path*, 1939, *ix*, 311

SYMPTOMATIC HEMOLYTIC ANEMIA *

By KARL SINGER, M D , and WILLIAM DAMESHEK, M D , F A C P ,
Boston, Massachusetts

IN their recent review of acute hemolytic anemia, Dameshek and Schwartz ^{7a} classify hemolytic anemia as follows

A Congenital

B Acquired

- 1 Secondary to known cause (infectious, chemical, "toxic," pregnancy, etc),
- 2 Symptomatic, in association with certain, usually malignant diseases, as lymphatic leukemia, Hodgkin's disease, carcinomatosis,
- 3 Of unknown cause, with or without hemolysins in the serum

Symptomatic hemolytic anemia may be defined as a hemolytic syndrome often indistinguishable by hematological methods from the well-known picture of familial hemolytic jaundice, but showing a definite etiological relationship to such underlying diseases as neoplasm (teratoma, sarcoma), leukemia, and Hodgkin's disease. Frequently but not regularly, the pathological lesions are situated in the spleen, thus suggesting a splenic disorder. That the hemolytic process in these cases is not merely coincidental is demonstrated, at least in some instances, by the disappearance of all signs of the hemolytic process following successful treatment of the "accompanying" disorder. Thus, removal of a dermoid cyst may result in complete cure of a severe hemolytic anemia. Furthermore, symptomatic hemolytic anemia has been observed in relatively few conditions.

The clinical features of the cases of symptomatic hemolytic anemia represent a combination of the symptoms and signs of the hemolytic process and those of the underlying disease. As the latter condition may remain latent or fail to manifest itself in characteristic fashion, the predominant picture may be that of the hemolytic process. On the other hand, the underlying disease may be readily apparent, but the "accompanying" hemolytic anemia may seem difficult to reconcile with the usual symptomatology. Since hemolytic anemia is by no means a common feature of most of the underlying disorders, it has on this account usually escaped attention. Why only certain cases of Hodgkin's disease with involvement of the spleen are associated with a hemolytic syndrome is quite obscure. The correct interpretation of these cases of symptomatic hemolytic anemia is of importance not only in the practical matters of diagnosis and therapy but in the more theoretical problems

* Received for publication March 27, 1941

From the Joseph H Pratt Diagnostic Hospital, and the Blood Clinic of the Boston Dispensary

Aided by grants from the Dazian Foundation, and the Charlton Fund, Tufts College Medical School

of the pathogenesis of inherited and acquired hemolytic jaundice. This paper, which deals with the analysis of several observations of symptomatic hemolytic anemia, illustrates these viewpoints.

I Symptomatic hemolytic anemia in association with neoplasm Anemia, which is common in neoplastic conditions, may be of several types. The hypochromic microcytic type of iron deficiency may be the result either of hemorrhage, impaired gastric digestion or of intestinal malabsorption. Another variety of anemia occasionally seen is that due to metastatic involvement of the bone-marrow, the anemia in this instance being normocytic and usually associated with the presence in the peripheral blood of nucleated red cells and immature leukocytes. Rarely, the typical macrocytic picture of pernicious anemia is observed in some cases of gastrointestinal neoplasm in which the pathological lesion interferes with the normal mechanisms of production, absorption or utilization of the anti-pernicious anemia principle.

Not generally known, however, is the fact that neoplasms, both benign and malignant, are occasionally associated with a hemolytic spherocytic process. The following two cases demonstrate this relationship.

Case 1 Dermoid cyst (teratoma) of the ovary T. P., a 47-year-old Jewish housewife, was admitted to the Joseph H. Pratt Diagnostic Hospital on May 8, 1939. Since the first of the year, she had noticed increasing pallor, weakness and dyspnea. Examination in May showed marked pallor and slight jaundice. There were arteriosclerotic changes of the retinal blood vessels, a rough blowing systolic murmur in the aortic area, and hypertension. Blood pressure: Systolic 198 mm of Hg, diastolic 108 mm. The edges of both the spleen and liver were just palpable. A mass the size of an orange was felt in the region of the left ovary.

The laboratory data were as follows: Hemoglobin 34 per cent, red blood cells 1.59 million, white blood cells 10,800, platelets 646,000. The red cells showed marked spherocytosis and the reticulocytes numbered 46 per cent. Three metamyelocytes and two myelocytes were noted in counting 100 white blood cells. The mean cell volume was 78 c. micra, the mean cell diameter 6.0 micra, the mean cell thickness 2.8 micra. Hemolysis in hypotonic solutions of NaCl began at 68 per cent and was complete at 40 per cent. The lysolecithin fragility test (Singer^{34a}) was normal. The urine contained no bile, but increased quantities of urobilinogen were demonstrated (1.80 by the Wallace-Diamond technic). The serum bilirubin, which was of the indirect variety, measured 5.0 mg. per 100 c.c.

On the basis of the spherocytosis and increased hypotonic fragility, the diagnosis of congenital or familial hemolytic jaundice was at first made despite the rather atypical and relatively acute onset, and the complete absence of familial hemolytic disease. The normal lysolecithin fragility was also against the familial type of disease. Splenectomy was advised.

The patient was admitted to the Beth Israel Hospital on June 28, 1939. The anemia was somewhat greater at this time, and nucleated red cells were commonly present (5-7 per 100 white blood cells). The spleen and liver were now felt two fingers'-breadth below their respective costal margins. After a single transfusion of 500 c.c. of blood, splenectomy was performed on July 6 under cyclopropane-ether anesthesia. A second transfusion was given postoperatively. Atelectasis of the left lower lung occurred the day after operation. A third transfusion was given on July 23 because the hematological response was unexpectedly slow.

By September 6, two months after operation, the red cell count had reached 4.19 million, the hemoglobin 77 per cent, and there had been striking drops in the reticulo-

cytes (45 per cent) and in the bilirubin content of the blood (to 0.9 mg per cent). This improvement was short-lived, however, for in October, 1939 the patient again began to feel poorly. She was readmitted to the hospital on November 24. Examination showed jaundice of the sclerae and skin and a greatly enlarged liver which was now palpable four fingers' breadth below the right costal margin. There was a striking drop in the red cell count—to 1.24 million—and in the hemoglobin to 24 per cent. Various procedures, such as the intravenous injection of congo red, roentgen-radiation over the abdomen, the use of large doses of liver extract and iron, were without effect. Because of the possibility of the presence of an accessory spleen, thorotrast (75 cc) was injected and roentgen-ray pictures taken, but no accessory spleen was demonstrated. The patient's course was steadily downhill and was interrupted only by repeated blood transfusions. In all, 24 transfusions, each of 500 cc, were given in the period from November 24, 1939 to February 29, 1940 with only transient rises in hemoglobin and erythrocyte counts. The last series of transfusions brought the level of erythrocytes to 3.4 million and the hemoglobin to 68 per cent. At this point, it was decided that further temporizing was inadvisable and that active search must be made either for an accessory spleen or, in view of the previous observation of West-Watson and Young,⁴⁰ for a dermoid cyst of the ovary. An exploratory laparotomy was accordingly done on February 29, 1940. No accessory spleen was found, but a large round mass arising from the left ovary was discovered and removed, together with the accompanying tube. Biopsy of the liver was also performed. Following this operation, the hemolytic process gradually subsided and in about four months the hematological picture was entirely normal. Spherocytosis and the increased hypotonic fragility of the erythrocytes disappeared completely, coincidentally with an increase in the mean cell diameter from about 6 micra to 7.35 micra. The blood bilirubin content dropped to normal and the urobilinogen excretion in the feces, which had approximated 2000 mg daily in December, also became normal (86 mg per day).

The ovarian mass proved to be a thick-walled, unilocular dermoid cyst, 7 cm in diameter, with a fairly smooth, pink-gray to bright pink inner membrane. In one area a rough, irregular, bony area 3 by 4 cm in extent was found. The cyst contained thick, mayonnaise-like fluid within which was found a small tangled skein of long brown hair. The relatively large area of well-formed bone showed a small amount of tissue closely simulating bone marrow. Also present were a few dilated sweat glands, cholesterol clefts, a large mass of fat, phagocytes sprinkled with plasma cells and large mononuclear cells, and half a dozen typical lymphoid follicles each of which had an active germinal center. No definite splenic tissue was discovered. Biopsy of the liver showed infiltration of the portal spaces with large numbers of lymphocytes, definite proliferation of bile ducts, together with areas in the sinusoids containing many polymorphonuclear leukocytes. The most marked change was the increased prominence of the Kupffer cells which were filled with hemosiderin.

This case thus appears to be an example of "symptomatic" hemolytic anemia which was temporarily improved by splenectomy but in which a cure was obtained only after removal of a dermoid cyst. We believe that the complete, and thus far permanent response up to Aug. 1941 points to a definite relationship between the hemolytic process and the dermoid cyst. A strikingly similar observation was made in the case of West-Watson and Young (1938).¹⁰ In this case, that of a 44 year old woman, there was a severe hemolytic anemia (hemoglobin 17 per cent, red blood cells 0.5 million, reticulocytes 50 per cent, marked spherocytosis and increased hypotonic fragility 0.66-0.44). There was an elevation in the bilirubin content of

the blood which was of the "indirect" variety. Splenectomy was performed but without subsidence of the hemolytic process. Operation for the possible removal of an accessory spleen was performed and an ovarian tumor discovered, as in our case. This proved to be a teratoma, and following its removal, the patient made an uneventful and complete recovery. No splenic tissue was found in the tumor.

TABLE I

Date	R B C Million per cu mm	Hgb %	Reticulocytes %	Hypotonic Fragility Hemolysis Begins — Complete	Remarks
5/ 8/1939	1.59	34	46	0.68 — 0.40	Many spherocytes
6/29/ "	1.66	33	33	0.68 — 0.04	Many spherocytes and normoblasts
7/ 7/ "	1.82	38	33	0.68 — 0.04	
7/ 7/ "				<i>Splenectomy</i>	
7/ 8/ "	1.93	44	36	—	Howell-Jolly bodies
7/14/ "	2.54	43	16.5	0.68 — 0.16	
7/31/ "	3.16	58	10	0.72 — 0.04	Marked spherocytosis
8/17/ "	3.64	67	8	0.72 — 0.22	Marked spherocytosis
9/ 6/ "	4.19	77	4.5	0.80 — 0.28	Marked spherocytosis
10/15/ "	2.89	58	6	0.64 — 0.04	
11/24/ "	1.24	24	12.5	0.68 — 0.04	Many nucleated red cells
11/28/ "	2.24	40	10.5	0.72 — 0.24	and spherocytosis
12/11/ "	2.03	42	8	0.72 — 0.24	
12/19/ "	1.51	28	16	0.68 — 0.26	
1/22/1940	2.29	46	10	0.68 — 0.24	Improvement due to repeated transfusions
2/16/ "	3.41	68	2.6	—	
2/29/ "				<i>Salpingo-oophorectomy</i>	
3/ 8/ "	2.50	47	5.6	0.68 — 0.16	Spherocytosis
3/15/ "	2.94	60	17	0.64 — 0.04	Many nucleated red cells
4/12/ "	4.31	76	2.6	0.60 — 0.12	and spherocytes
5/10/ "	5.04	101	1.7	0.52 — 0.12	Spherocytes very rare
6/28/ "	5.52	102	0.9	0.50 — 0.16	Spherocytes very rare
7/ 5/ "	5.38	102	2	0.46 — 0.12	No spherocytes
8/ 7/ "	4.98	96	2.7	0.44 — 0.12	No spherocytes
6/30/41	5.04	95	1.0	0.42 — 0.12	Red cells normal

A somewhat similar case is reported by Suarez and Etcheverry (1937)³⁵. In this instance a dermoid cyst arising from the splenic hilus was discovered. Splenectomy, together with removal of the tumor, was performed but the patient unfortunately died shortly after operation. Definite relationship of the tumor to the hemolytic anemia was thus not established.

The coexistence of a dermoid cyst and hemolytic anemia does not necessarily indicate an etiologic relationship. This is illustrated by an observation of Watson^{38a}. In this case, that of a 19 year old girl, hemolytic anemia in association with a large ovarian cyst was present. The laboratory findings were as follows: Hemoglobin 32 per cent, red blood cells 1.15 million, white blood cells 6000, reticulocytes 15 per cent, hypotonic fragility normal, icterus index 42, "indirect" bilirubinemia. The anemia was of the macrocytic variety. The daily fecal urobilinogen excretion was 1106 mg, indicative of a severe hemolytic process. Marked auto-agglutination of the red cells was observed. Oophorectomy was performed without result, but when splenec-

tomy was then done, there was a very slow, steady improvement which finally led to complete recovery. This observation indicates that a dermoid cyst is not necessarily in and of itself the entire cause of a hemolytic process, but that it might have a definite relationship nevertheless. It is possible that these cases may require removal of both the tumor and the spleen.

Case 2 Lymphosarcoma arising within the pancreas A R., a 50-year-old Jewish merchant with a completely negative past history, complained of fever of several weeks' duration, dyspnea, and progressive weakness. During the two weeks prior to admission to the hospital he had noticed slight jaundice, together with severe and cramp-like mid-abdominal pain radiating to the left costovertebral region. Examination showed an emaciated man with a yellowish tint of the skin and sclerae. Neither the liver nor spleen was palpable. There was distinct tenderness in the left costovertebral region. The laboratory data were as follows: urine negative for albumin, sediment normal, no bilirubin, greatly increased quantity of urobilinogen, blood—hemoglobin 40 per cent, red blood cells 1.9 million, white blood cells 22,000, reticulocytes 28 per cent, anisocytosis, poikilocytosis and marked spherocytosis, hypotonic fragility 0.60–0.28 per cent, differential count of the leukocytes, marked "shift to the left." The icterus index was 40, and the bilirubinemia was of the indirect variety. Roentgen-rays of the kidneys were normal, but a gastrointestinal series showed an indentation along the posterior wall of the stomach, due probably to an extrinsic mass. Laparotomy was performed, and a tumor the size of a lemon arising from the middle third of the pancreas was found. The tumor, which was separated from the pancreas by a thick capsule, was completely removed. Unfortunately the patient died 24 hours after operation. Sections of the tumor showed a "round cell" (lympho-) sarcoma with areas of necrosis*.

Although no definite proof is present regarding the symptomatic character of the hemolytic anemia in this case, the completely negative family history and the simultaneous development of the hemolytic process with the symptoms of the neoplasm are in favor of this view. Similar observations have been made by Thompson^{36a, 36b} hemolytic anemia in three cases of sarcoma of the spleen, Waugh³⁹ hemolytic anemia with increased hypotonic fragility in two cases of carcinoma with metastasis to the bone-marrow, and Caioli and Lavergne⁶ acute hemolytic anemia with metastatic bone marrow involvement from primary carcinoma of the stomach.

Although the reports of hemolytic anemia in association with malignant neoplasms are few in comparison with the great frequency of these disorders, it is possible that this is due in part at least to the relatively little attention which is paid to the type of anemia in a given case of malignancy. In other words, anemia if present is said to be "secondary," and given scant attention. The mechanism responsible for the sudden development of the hemolytic process in a case of neoplastic disease is at present obscure, although the possibility is present that some sort of hemolysin is produced (*vide infra*).

II Hemolytic anemia in Hodgkin's disease The usual type of anemia found in cases of Hodgkin's disease is of the hypochromic variety, it is usually mild, and of great severity only in the terminal phases of the disease.

* This case was seen by one of us (K. S.) in Vienna in 1934. A complete histological description of the tumor is unfortunately not available.

Occasionally, due to invasion of the marrow, a normocytic anemia may be seen. Rarely, hemolytic anemia may be present, as in the case reported below.

Case 3. M. L., a 45-year-old woman, had developed cervical adenitis 18 years previously. At biopsy the diagnosis of tuberculosis was made. Six years prior to the present illness a mediastinal tumor was discovered and treated with roentgen-rays. Three months before admission to the hospital the patient developed fever, slight jaundice, weakness, dyspnea on exertion, and increasing pallor. Examination showed slight jaundice and a readily palpable spleen. There was no peripheral lymphadenopathy but a large mediastinal mass was found on roentgen-ray examination of the chest. The laboratory data were as follows: urine, no bilirubin, urobilinogen greatly increased, blood, hemoglobin 52 per cent, red blood cells 1.8 million, white blood cells 12,600, reticulocytes 12.6 per cent. There was marked anisocytosis, poikilocytosis and spherocytosis. The hypotonic fragility was 0.60–0.35 per cent, but the lysolecithin fragility was normal on two occasions. Examination of the relatives (mother and two children of the patient) was completely negative for the presence of hemolytic jaundice. The diagnosis of symptomatic hemolytic anemia was made and splenectomy advised despite the presence of Hodgkin's disease. Operation revealed the typical "porphyric" spleen of the disease. Following operation there was improvement in the anemia, which then became hypochromic: hemoglobin 50 per cent, red blood cells 3.5 million, color index 0.7. The patient felt much better for about five months, following which large masses of cervical lymph nodes appeared, and shortly afterwards the patient died. Postmortem examination was not obtained.

The occurrence of hemolytic anemia in Hodgkin's disease has been repeatedly observed. The first case was described by Holler and Paschkis (1927)¹⁹ who splenectomized a patient with hemolytic anemia without any clinical evidence of Hodgkin's disease, but found to their surprise a porphyric spleen. Singer (1936)^{34c} described a case and summarized 13 cases from the literature. Other cases not described in Singer's article are those of Kwaszewska,²⁵ Watson (three cases),^{38a} Schiapoli,³² Bruins Slot,⁵ and v. Brattenberg.⁴ The spleen was involved in almost all of the cases, and in some (Holler and Paschkis,¹⁹ Gripwall,^{14a, b} Singer^{34c}) splenectomy led to a temporary improvement with complete disappearance of the hemolytic anemia which was later replaced by a hypochromic microcytic anemia. The almost constant involvement of the spleen together with the effect of splenectomy in some of the cases suggests that a primary splenic disorder may be responsible for the development of the hemolytic process. Against this interpretation is an observation by v. Brattenberg⁴ in whose case the spleen showed none of the pathological lesions of Hodgkin's disease. Davidson,^{8b} Parkes Weber and E. Schwarz,²⁸ Watson^{38a} and others have pointed out that the anemia in these cases is of the macrocytic variety. Dameshek and Schwartz^{7a} believe, however, that the macrocytosis is more apparent than real ("pseudo-macrocytic"). They are of the opinion that the macrocytosis of certain cases of hemolytic anemia is due to the presence of numerous reticulocytes, which are much larger than the mature orthochromatic red cells. The hypotonic fragility of the erythrocytes in most of the cases was increased but in some cases was normal (Gripwall,^{14b, 14c} Bensis and Gout-

tas²) Again, the mechanism resulting in the development of the hemolytic process is obscure

III Hemolytic anemia in leukemia Anemia is a very common finding in chronic lymphatic and myelogenous leukemia. Usually it is normocytic and due to replacement of the erythropoietic tissue in the bone marrow by the proliferating process. Occasionally, however, a typical hemolytic syndrome with jaundice, spherocytosis and increased hypotonic fragility may be present. We have observed two such cases

Case 4 F. C., a 70-year-old man, was admitted to the hospital October 27, 1938 in a semicomatose condition. The history as obtained from a daughter revealed that the patient had been healthy until five years previously when mild diabetes was discovered. On the day before entry he was apparently well and without jaundice. The following day his son noted that he walked with a heavy shuffling gait, and that he looked weak and yellowish. He complained of weakness and nausea. Immediately prior to admission to the hospital he was quite rational, he shortly became extremely weak, suddenly became semicomatose and began to vomit. Examination revealed an elderly, moribund man with marked pallor and moderate jaundice, the liver and spleen were readily palpable. One large lymph node in the right axilla and several small inguinal nodes were felt. The laboratory findings were as follows: hemoglobin 36 per cent, red blood cells 2.4 million, white blood cells 105,000 (1). The platelets were abundant. The smear showed extreme lymphocytosis (polymorphonuclear neutrophils 8, lymphocytes 92, monocytes 0), the lymphocytes being almost all of the mature variety. The red cells showed very marked spherocytosis which was well brought out in the fresh preparations. The hypotonic fragility was 0.72–0.28 per cent, with a normal lysolecithin fragility. The reticulocytes numbered 8.3 per cent. An occasional nucleated red cell was seen. The bilirubin content of blood was 4.2 mg per 100 cc, with an indirect van den Bergh reaction. The urine contained albumin and sugar, but no bilirubin, and the urobilinogen content was 1.80. The blood sugar was 482 mg per cent, the non-protein nitrogen 78 mg per cent, and the CO₂ combining power 31.8 volumes per cent. A diagnosis of chronic lymphatic leukemia, acute hemolytic anemia, and diabetic coma was made. Despite treatment with insulin and two blood transfusions, the patient died the same day. At postmortem examination the liver weighed 2490 gm and showed histologically large accumulations of mature lymphocytes in the portal areas without a corresponding increase in the periportal connective tissue. The spleen, which weighed 620 gm, showed large masses of mature lymphocytes in the pulp with complete effacement of the normal splenic architecture. There was generalized enlargement of lymph nodes, particularly marked in the mesentery. Microscopic examination revealed massive lymphocytic infiltration and proliferation in the pulp and sinuses with some infiltration of the connective tissue capsule and the adjacent fat. The bone marrow was pinkish gray, very hyperplastic, and greatly infiltrated with lymphocytes. Slight normoblastic hyperplasia was noted.

Case 5 Louis F., a 57-year-old Jewish photographer, noticed "lumps" in his neck and a mass in the left upper part of his abdomen approximately 8 to 10 years before admission to the Pratt Diagnostic Hospital on November 15, 1940. About a year prior to admission a physician found generalized lymphadenopathy, well-marked splenomegaly, a leukocyte count of 200,000 per cu mm with 99 per cent lymphocytes. He was referred to the Tumor Clinic of the Boston Dispensary for treatment and in March, 1940 was given four roentgen-ray treatments of 25R each to the entire body ("spray"). Although the hematological response was quite satisfactory, the leukocyte count dropping from 367,000 to 14,000, the patient developed a severe reaction in the form of weakness, fatigue, anorexia, vomiting, and marked loss in weight.

From that time on the course was unsatisfactory. A month later, in April, 1940, a generalized eruption resembling varicella appeared, histologically, the lesions were typically leukemic. The leukocyte count gradually rose to over 200,000 and on October 5 and 8, 1940 he was given two roentgen-ray treatments of 150R each over the spleen. He complained of vomiting and diarrhea, and intermittent jaundice gradually became apparent. He rapidly became weaker and paler, although there was some regression in the size of his lymph nodes and spleen. Within a period of five weeks or less, the red cell count dropped from 304 million to 171 million. There was then slight improvement, but in the two weeks prior to admission to the hospital, the red count rapidly fell from 254 million to 086 million.

Examination on admission November 15, 1940 revealed a very thin, pale, slightly icteric man. The temperature was 101° F, the pulse 100 per minute. There was generalized lymphadenopathy, the glands being firm, discrete, and measuring 3 to 8 cm in length. The spleen was felt 15 cm below the left costal margin, and the liver was felt 10 cm below the right costal margin.

The laboratory data were as follows: Urine: slight trace of albumin, no bilirubin, urobilinogen greatly increased; Stools: dark color, daily fecal urobilinogen output (four day sample) 225 mg per day, approximately five times normal for the red count; Blood: Hemoglobin 24 per cent, red blood cells 086 million, hematocrit 12 per cent, M C V approximately 130 c micra, white blood cells 155,000, Differential Count: polymorphonuclear neutrophils 3 per cent, lymphocytes 93 per cent, monocytes 4 per cent, Platelets 93,000, Reticulocytes 33 per cent. The blood picture was "pseudo-macrocytic" in type, i.e., the large numbers of reticulocytes present resulted in apparent macrocytosis. Careful examination of the mature erythrocytes, however, disclosed that they were for the most part smaller than normal and that many spherocytes were present. The hypotonic saline fragility was 52 per cent beginning hemolysis and 28 per cent complete hemolysis (control 44-24 per cent). The lysolecithin fragility was normal. The serum bilirubin was 9 mg per 100 cc, and of the indirect variety.

Three transfusions of 500 cc of blood were given with slight improvement. On December 5, hemoglobin was 40 per cent, red cell count 162 million, reticulocytes 33 per cent, platelets 32,400, leukocyte count 75,000 (lymphocytes 94 per cent). There were fewer spherocytes. The question of splenectomy was discussed, but the idea was quickly abandoned in view of the marked involvement of the bone marrow with lymphoid tissue as determined from sternal puncture and trephine biopsies.

The possibility that the roentgen-ray treatments directed over the spleen were in some measure responsible for the development of the hemolytic anemia in this case of chronic lymphatic leukemia must be considered. Certain it is that prior to the roentgen-ray treatments, the patient was in moderately good condition, directly following the first series (spray therapy), he felt poorly, lost considerable weight, and developed a leukemic rash. Following the second series which was given over the spleen, he developed hemolytic anemia.

The occurrence of a well-defined hemolytic syndrome in chronic lymphatic or myelogenous leukemia is rare, although it has been repeatedly observed (cases have been reported by Haden,^{13a} Paschkis,²⁰ Watson,^{33a} Marchall, Dany and Grupper,²⁶ Troisier and Tixier,³⁷ Klima,²² and Singer^{34a}). In Haden's case, splenectomy was performed on the assumption that an idiopathic process was present. The hemolytic process continued unabated and

six months later the typical features of chronic lymphatic leukemia became evident

Rhoads³⁰ has recently emphasized a hemolytic component which he states is frequent in "refractory" or "aplastic" anemia. Included in this rather heterogeneous group with a common denominator of severe normocytic anemia, leukopenia, and thrombocytopenia are a number of cases of aleukemic leukemia and atypical or generalized Hodgkin's disease. We have recently observed two such cases in which mild icterus and increased fecal urobilinogen output were present in addition to the severe anemia.

In one (R F), chronic aleukemic myelogenous leukemia was present with the following blood counts: hemoglobin 42 per cent (6.5 gm), red blood cells 2.25 million, white blood cells 3400, platelets 657,000, reticulocytes 3.0 per cent, polymorphonuclear neutrophils 35 per cent, lymphocytes 61 per cent, monocytes 1 per cent, eosinophils 3 per cent. The hypotonic fragility was 48-20 per cent. Blood bilirubin was 1.6 mg per 100 cc (indirect reaction), icterus index 12 units, and daily fecal urobilinogen output 223 mg (about two to three times the normal value for the patient's red cell count).

In another case (O H), with aleukemic reticulosis, the following blood counts were present: hemoglobin 46 per cent, red blood cells 2.52 million, white blood cells 4300, platelets 277,000, reticulocytes 3.3 per cent. On January 3, 1941, there was no appreciable icterus but the blood bilirubin was 1.7 mg. From January 16 to January 25, the patient received seven "spray" roentgen-ray treatments of 25R each. On February 3, the sclerae were definitely icteric and the blood bilirubin content was 1.5 mg. Studies of the fecal urobilinogen were not done.

Watson^{38a} has emphasized the macrocytic character of the hemolytic anemia in leukemia. In our first case there was marked spherocytosis without macrocytosis, in the second case, spherocytosis was not a striking phenomenon, although it became readily evident when the rate of hemolysis became greatly increased. Before this was apparent, the anemia was superficially macrocytic, although careful analysis of the cell diameters of both the reticulocytes and non-reticulocytes demonstrated the "pseudo-macrocytic" character of the anemia.

Possibly related to the cases of hemolytic anemia in leukemia are those in association with Boeck's sarcoid and giant follicle lymphoma. Haden^{15a} has described an interesting case of hemolytic anemia in which a probable sarcoid involving both lungs was present. The spleen was not enlarged. Roentgen-radiation of the pulmonary process resulted in disappearance of both the sarcoid and the hemolytic process. Haden^{15a, b} stated that although the exact cause of the hemolysis was not clear, it was probably due to some toxin incidental to the primary disease in the lung. At the Mt Sinai Hospital (N Y)* a case was recently observed in which there was generalized lymphadenopathy, extreme splenomegaly, and hemolytic anemia. Biopsy of one of the nodes demonstrated giant follicle lymphoma. Following roentgen-ray therapy to the spleen and lymph nodes, there was definite im-

* Personal communication from Dr. Louis R. Wasserman, who will report this case in detail.

provement in the anemia and jaundice and diminution in the output of urobilinogen

That the hemolytic process in all of these cases was in some manner dependent upon the abnormality of lymphoid apparatus is quite clear, although the exact mechanism for the destruction of the red cells is quite obscure (see below)

V Hemolytic anemia in liver disease In recent years increasing attention has been paid to the anemia associated with hepatic disorders. Except when hemorrhage or a complicating infection are present, the anemia is either normo- or macrocytic (Wintrobe,^{42a, b} Wright,¹³ Rosenberg³¹ and others). Eppinger,¹⁰ Fellingner and Klima,¹¹ and Watson^{38a, b} have emphasized the hemolytic character of this anemia as indicated by an increased output of fecal urobilinogen. There is frequently a rough parallelism between the severity of the anemia and the degree of liver damage. The blood picture resembles that of pernicious anemia more closely than it does that of hemolytic jaundice. Spherocytosis is not usually observed and the saline fragility is usually normal. Fullerton and Davidson,³⁴ however, report a case of macrocytic anemia in association with cirrhosis of the liver in which the hypotonic fragility was abnormal (starting at 0.7 per cent of NaCl), and Watson^{38a} concedes that the mean cell thickness of the red cells may be increased even in the presence of macrocytosis. From these and other data it may be concluded that the anemia of liver disease, although occasionally of hemolytic character, differs usually in many respects from the picture of symptomatic hemolytic jaundice as discussed in this paper. The following case demonstrates the occurrence of such a symptomatic hemolytic syndrome in liver disease.

Case 6 E. D. G., a 25-year-old housewife, was admitted to the J. H. Pratt Diagnostic Hospital on April 26, 1941, with the complaint of progressive anemia, jaundice, and weakness of about 3 years' duration. In May 1938, she had been delivered of twins, the pregnancy and childbirth were both uncomplicated, but shortly after delivery she became increasingly pale and weak. About 8 months after delivery her family physician treated her for anemia with large doses of iron and injections of liver extract. Since no relief ensued, she was hospitalized and given six transfusions of blood. There was only temporary relief and for the following two years she was studied and treated by various physicians and hospitals but continued to feel weak and dyspneic. Just prior to her first visit to the Blood Clinic of the Boston Dispensary, April 2, 1941, the diagnosis of Hodgkin's disease of the spleen had been made at another hospital and roentgen-ray therapy over the spleen had been given, also without relief. Following the roentgen-ray treatments which caused severe nausea and vomiting, there occurred a rather rapid increase in symptoms and the red cell count, which was 1.71 M per cu mm on April 2, had declined to 1.06 M on April 29. The remainder of the history was irrelevant, there was no family history of jaundice, anemia, or splenomegaly. Alcoholism was denied.

Physical examination on admission showed marked pallor, slight icterus, a normal appearing tongue, slight enlargement of the heart with a soft systolic murmur, an enlarged liver palpable 2 fingers' breadth below the right costal margin and a greatly enlarged spleen extending to the umbilicus. The blood findings were as follows: Hgb

27 per cent (42 gm), RBC 106 M, color index 13, WBC 2900, platelets 24 000, polymorphonuclear granulocytes 49 per cent (4 band forms), lymphocytes 26 per cent, monocytes 12 per cent, eosinophiles 12 per cent, basophiles 1 per cent. The mean corpuscular volume varied from 130 to 150 cu micra, the mean cell diameter was 85 micra (normal 75 micra), the mean cell thickness was 27 micra (22 micra high normal). The reticulocytes averaged 88 micra in diameter, and the mature orthochromatic red cells 82 micra. The reticulocytes varied between 19.5 per cent (April 2) and 49.5 per cent (May 1). The red cells showed marked changes in size, shape, and staining characteristics with polychromatophilic macrocytes outstanding. There was no spherocytosis. The hypotonic fragility test showed beginning hemolysis at 0.42 per cent of NaCl, and complete hemolysis at 0.20 per cent. The Ham acid fragility test was negative. The mechanical fragility of the red cells (Dameshek and Miller^{7d}) was definitely abnormal, 27 to 33 per cent hemolysis occurring after 3 hours of mechanical shaking with glass beads (normal value 5 to 7 per cent hemolysis).

The urine showed no bilirubin but contained greatly increased quantities of urobilinogen. The daily fecal urobilinogen output (average of 4 days output) was 1925 mg, approximately 25 times the normal value. The blood bilirubin was of the indirect type and measured 3.0 mg per 100 cc.

The gastric analysis showed the presence of free HCl. Roentgen-rays of the chest and long bones were negative. The sternal puncture showed extreme normoblastic hyperplasia, with a marked relative reduction in the leukocytes and megakaryocytes. The bilirubin excretion test (50 mg of bilirubin injected intravenously) showed 100 per cent retention of the dye, indicating definite hepatic damage. Tests of the serum for isohemolysins, autoagglutinins, and autohemolysins were negative.

Thus the various studies showed the presence of a severe, truly macrocytic anemia, leukopenia, thrombopenia, but a very marked reticulocytosis. The bone-marrow showed extreme erythroblastic hyperplasia and the fecal urobilinogen output indicated an unusually marked hemolytic process. Although the complete retention of the injected bilirubin pointed towards definite hepatic dysfunction, the significance of this observation was at first not appreciated. The patient was given three transfusions of blood from compatible donors and was then transferred to the Beth Israel Hospital for splenectomy. This, together with biopsy of the liver, was performed by Dr W. S. Levenson on May 13, 1941. The liver was grossly nodular and irregularly mottled in appearance. The spleen was extremely large, weighing 1960 gm. Histologically the liver showed a moderate amount of fibrous tissue within the portal areas and also thin bands of young fibrous tissue extending from the portal area to within the lobules in a fan-like fashion. In both types of fibrous tissue a moderately heavy sprinkling of inflammatory cells consisting mainly of lymphocytes and eosinophilic leukocytes was demonstrable. No evidence of abnormal hematopoiesis was present. Diagnosis sub-acute hepatitis. The spleen showed histologically a marked diminution of lymphocytes within the pulp, some giant cells probably of reticulum cell origin, and hematopoietic activity which appeared to be limited to the cells of the granulocytic series.

The patient made a complete uneventful recovery. Without further transfusions, there was an almost immediate increase in Hgb and red cell count and a concomitant decrease in bilirubin and reticulocytes. On May 20, Hgb was 46 per cent, RBC 217 M, reticulocytes 4.2 per cent and serum bilirubin 0.6 mg. On June 9, Hgb. was 57 per cent, RBC 332 M, WBC 8000, reticulocytes 3 per cent, platelets approximately 15 M and serum bilirubin 0.6 mg. On July 14, the Hgb had risen to 74 per cent and the red cell count to 35 M. The MCV and MCD remained elevated, however, at 109 cu micra and 83 micra respectively, indicating persistent macrocytosis. The hypotonic fragility was 0.40 to 0.04 per cent.

The persistence of moderate anemia in association with macrocytosis and the finding of severe liver disease indicated that the residual macrocytic anemia was on

the basis of hepatic disease. However, the hemolytic component was now completely absent, as evidenced by the return to normal values of the blood bilirubin, the reticulocytes and the fecal urobilinogen output. This indicated that although the hemolytic process was secondary or symptomatic of the hepatic disease, it was nevertheless primarily splenic in origin. Something abnormal within the spleen had resulted in increased blood breakdown, which could only be relieved by splenectomy.

VI Hemolytic anemia in infectious diseases Hemolytic anemia is occasionally observed in the course of various infectious diseases. Widal, Abramí and Brulé¹¹ listed malaria, streptococcic and staphylococcic infection, tuberculosis, anaerobic organisms including *B. Welchii*, and ankylostomiasis as possible causes. That toxic substances of non-bacterial origin may also produce hemolytic anemia has become generally known from observations of the untoward sequelae occurring with sulfanilamide administration (Kohn,²¹ Harvey and Janeway,¹⁷ and others). The same effect may be produced by lead (Davidson,^{8b} Aub, Fairhall, Minot and Reznikoff¹), phenylhydrazin (Kaminer and Rohnstein²²), etc. Strictly speaking, these "drug anemias," although they often present spherocytosis, etc. (cf Dameshek and Schwartz²³), do not belong in the group of symptomatic hemolytic anemias as defined in this paper. The symptomatic hemolytic anemias of infectious diseases disappear if the underlying disease is successfully treated, thus again demonstrating a causal relationship. This was observed in the following case.

Case 7 M. L.,* a 62-year-old man, developed an acute febrile illness and on admission to the hospital four days later was found to have complete consolidation of the left lower lung. The temperature was 105° F, the pulse 120, and the respirations 40 per minute. Slight jaundice and marked pallor were also noted. The laboratory findings were as follows: hemoglobin 41 per cent, red blood cells 1.2 million, white blood cells 38,900. The blood smears showed moderate spherocytosis, and many nucleated red cells. The hypotonic fragility was 0.54-0.42. The urine showed slight albuminuria but no bile. The total protein of the blood was 6.7 gm per cent. The sputum showed a type 17 pneumococcus. Serum bilirubin was indirect and measured 4.6 mg per 100 cc. The unusual feature of the case was the presence of a very strong panagglutinin in the blood. It was at first impossible to perform red cell counts because of marked agglutination in the pipettes. The erythrocytes of 36 successive donors were agglutinated by the serum of the patient. Dilution of the serum was without effect. Finally, compatibility tests were performed by incubating the blood at body temperature, following which the patient was transfused without incident. Treatment with sulfapyridine and specific Type XVII antipneumococcic serum was instituted. The panagglutinin gradually diminished in intensity. With subsidence of the pneumonic process, there was a gradual rise in the red cell count to 3.0 million, hemoglobin to 53 per cent. With complete recovery, the autoagglutinin disappeared entirely and the blood levels became normal.

It is possible that the hemolytic anemia in this case was induced by intravascular agglutination resulting from the activity of the autoagglutinin. Another possible interpretation is that the autoagglutinin indicated the pres-

* This case is reported through the kindness of Dr. Joseph E. Porter and Dr. Mortimer C. Warren of Portland, Maine.

ence of an associated hemolysin. Hemolytic substances of the immune body type have recently been described by Dameshek and Schwartz^{7a, b} in acquired hemolytic anemia of the idiopathic type. Whether the present case was one of acute idiopathic hemolytic anemia with accompanying pneumonia or whether the pneumonia was responsible for the hemolytic anemia is not clear. Since both processes began and disappeared simultaneously the latter relationship seems probable.

Symptomatic hemolytic anemia in association with a tuberculous process of the spleen has recently been described by Engelbreth-Holm.⁹ In tuberculosis of the spleen the anemia is usually normochromic to hyperchromic (Howells²⁰), but in Engelbreth-Holm's⁹ case the anemia was typically spherocytic: hemoglobin 45 per cent, red blood cells 2.0 million, color index 1.15, vol. index 1.17, reticulocytes 37 per cent, leukocytes 16,700, hypotonic fragility 0.80–0.04, icterus index 20. Splenectomy was performed, but the patient died of thrombosis of the inferior vena cava. There was no evidence of congenital or familial jaundice. Thompson^{36a} also reports a case of "atypical hemolytic anemia" with caseous tuberculosis of the spleen and lymph nodes. Giffin¹³ (1919) described two cases of primary tuberculosis of the spleen with hemolytic jaundice. There was no evidence of familial hemolytic disease. In one, the hypotonic fragility was increased. Splenectomy was performed in both and was followed by complete recovery. Although Engelbreth-Holm does not relate the hemolytic anemia to the tuberculous involvement of the spleen, Giffin¹³ discusses this possibility, and indeed such a relationship seems quite possible.

DISCUSSION

1 Diagnosis and Differential Diagnosis The diagnosis of symptomatic hemolytic anemia may be very difficult, especially since the syndrome is not at present well-known. Diagnosis of the hemolytic component (i.e., increased blood destruction) should at least be suspected from the presence of jaundice in association with pallor, and in the absence of bile from the urine. The spleen is furthermore palpable in most cases. Further study will reveal bilirubinemia with an indirect van den Bergh reaction, normal or dark-colored feces with greatly increased output of urobilinogen, and usually an increase in the urinary urobilinogen. Spherocytosis, if carefully looked for, should be recognizable in most cases in both fresh and stained preparations. The contrast in appearance between these small, dense-appearing cells and the large reticulocytes is striking. All the evidences of increased regenerative activity on the part of the marrow are also present, i.e., reticulocytosis, polychromatophilia, nucleated red cells, polymorphonuclear leukocytosis, immature granulocytes, and thrombocytosis. The bone marrow itself (sternal puncture) shows extreme hyperplasia, particularly of the erythroblastic elements. When the definite diagnosis of a hemolytic process has been made,

the case must be further analyzed. The hemolytic processes may be subdivided into three large groups.

First pernicious anemia must be considered. In this condition there is a true macrocytic anemia, the mature orthochromatic red cells being larger on the average than normally. This is quite in contrast with the "pseudomacrocytic" hemolytic processes in which the only large erythrocytes are the immature polychromatophilic reticulocytes. Gastric analysis reveals complete achlorhydria with histamine, whereas our hemolytic cases tested showed the presence of free HCl. The sternal puncture in pernicious anemia reveals a characteristic megaloblastic hyperplasia with the presence of bizarre giant metamyelocytes. There is, furthermore, the therapeutic test with liver extract, which, by the way, has usually been performed before the hematological consultant sees the case. With all these criteria in mind, the differential diagnosis between the "liver extract" deficiency state known as pernicious anemia and hemolytic anemia is usually not a very difficult procedure.

The second group comprises a heterogeneous group of hemolytic syndromes including the congenital and acquired idiopathic hemolytic anemias, and such conditions as sickle-cell anemia, Cooley's erythroblastic anemia, and the Marchiafava-Micheli syndrome of paroxysmal nocturnal hemoglobinuria. In the congenital condition, a careful familial history and hematological study of the family members may reveal other cases. It should be noted, as Dameshek and Schwartz^{7a, b} have repeatedly stated, that spherocytosis and increased hypotonic fragility are by no means pathognomonic of the hereditary type, but are commonly seen in acquired cases. The lysolecithin fragility test (Singer^{34a}) may be of aid in differentiating these two conditions, since the erythrocytes of the congenital type are more fragile to this lysin than those of the acquired variety. Isohemolysins and autoagglutinins should always be searched for since they are seen only in the acquired type.

Sickle cell anemia and Cooley's anemia should be readily diagnosed if the racial background, the presence of target cells (Haden and Evans,^{15d} Dameshek^{7c}), the reaction of the erythrocytes to incubation in the case of sickle cell anemia, the decreased saline fragility, and other factors (bone changes, etc.) are taken into account. The Marchiafava-Micheli syndrome is characterized by nocturnal hemoglobinuria and a chronic hemolytic anemia which according to Ham^{16a} resides in a fundamental abnormality of the red blood cells. Spherocytosis is completely lacking and the hypotonic saline fragility is normal, although the "acid" fragility test (Ham) is positive. Splenectomy is furthermore completely without effect.

The third group consists of all hemolytic anemias of known etiology, i.e., those due to drugs, allergic reactions, as well as to various fundamental underlying conditions, i.e., symptomatic. The drug anemias may show an almost identical picture with acute hemolytic anemia, with complete subsidence upon cessation of the administration of the drug. Allergic hemolytic anemia is represented by favism, a condition which is apparently found

only in certain areas of Italy following contact with the fava bean plant. The mechanism of this condition is quite obscure. If all these conditions have been ruled out, the presence of symptomatic hemolytic anemia should then be considered, although ordinarily the situation presents itself in the reverse manner, i.e., the diagnosis of a hemolytic process has been made. Is it idiopathic or is it bound up with some underlying condition? This should always be searched for.

The diagnosis of the symptomatic form of hemolytic anemia is based first on the knowledge that this syndrome may occur in the presence of the several conditions as described in this paper and secondly on the symptomatology of the various underlying disorders. Hemolytic anemia which is symptomatic of Hodgkin's disease, lymphatic leukemia, lymphosarcoma, and giant follicle lymphoma, may be readily diagnosed in the presence of a relapsing fever (Pel-Ebstein type), lymphadenopathy, a characteristic blood picture, or the roentgen-ray findings of a mediastinal mass. However, when these indications are lacking, search should always be made in an apparently idiopathic hemolytic process for evidences of tumor, destructive bone lesions indicative of metastatic lesions, and invasion of the bone marrow. Thus in addition to a careful physical examination and roentgen-ray of the chest, roentgen-rays of the bones and sternal puncture are indicated in a hemolytic process to make reasonably certain that it is not "symptomatic." Even with all care, however, there will be occasional cases diagnosed as "idiopathic" which will eventually prove to be "symptomatic" in nature. This occurred in Case 1 (dermoid cyst of the ovary), and in Case 6 (severe liver disease). Haden^{15b} also emphasizes this point in describing a case of what was apparently congenital or acquired hemolytic anemia but which failed to improve after splenectomy, chronic lymphatic leukemia was the final diagnosis. If a case of apparently "idiopathic" hemolytic anemia fails to respond or relapses after splenectomy, the possibility of an underlying disease which has been overlooked should be seriously considered and searched for. To summarize, the diagnosis of hemolytic anemia per se should now be made more frequently than in the past, especially when it is realized (a) that the designation of "secondary anemia" is meaningless, (b) that even slight icterus may be indicative of a hemolytic process. When the latter is discovered, appropriate measures must be taken to classify the hemolytic process as accurately as possible. In this way, the occasional case of hemolytic anemia due to an underlying disease will be recognized.

The prognosis of symptomatic hemolytic anemia depends on the underlying disease. If this disease is curable, the prognosis may be excellent. This is illustrated by Case 1 (dermoid cyst). Otherwise, the effect of splenectomy is by no means certain. There may be a temporary improvement in the hemolytic process, or even complete disappearance with a change to the more usual hypochromic type of anemia, or there may be no effect whatever. It is always advisable, if at all possible to remove or ameliorate

the underlying disease before splenectomy is performed. As stated above, in order to effect a cure in a given case, it may be necessary to remove both a tumor such as a dermoid cyst and the spleen. These points, however, are not yet clear, and must await further observations.

2 Pathogenesis The hematological picture of symptomatic hemolytic anemia is frequently identical with the "idiopathic" types—both inherited and acquired. This might indicate that similar pathogenetic mechanisms are at the basis of these disorders. A rough analogy with pernicious anemia may serve for illustration. In this disease, we have learned, chiefly through Castle's investigations, that the anemia develops if the physiological mechanisms of production, absorption or utilization of the antipernicious principle are disturbed by various pathological processes. In this way, the "symptomatic" types of pernicious anemia (i.e., those cases in which the fundamental abnormality was an organic lesion of the stomach or bowels) have become readily understood. Until the discovery of the efficacy of liver therapy, one of the few cases of pernicious anemia known to be permanently cured was associated with chronic ulceration of the small intestine (Seydewitz³³), upon resection of the lesions, the blood picture became permanently normal. Today the pathogenesis of this particular case of "symptomatic" pernicious anemia is interpreted as due to malabsorption of the anti-anemic principle. In hemolytic anemia, we may conclude by analogy that the pathogenesis of the symptomatic types may be explained on the basis of theories already extant concerning the "idiopathic" varieties.

Considerations regarding the pathogenesis of "idiopathic" hemolytic anemia are bound up with (1) the presence of spherocytosis and the associated increase in hypotonic saline fragility, and (2) the effect of splenectomy in the amelioration of this disorder. Although many different opinions are present regarding pathogenetic mechanisms, the outstanding ones are those postulating a faulty bone marrow, an increase in hemolysin production, or an abnormality of the spleen.

The theory of a faulty production of erythrocytes in the bone marrow was first proposed by Naegeli²⁷ who claimed that splenectomy did not alter the production of spherocytes by the marrow but simply removed the inhibitory effect of the spleen on the bone marrow. Following splenectomy, and despite the continued presence of spherocytosis, there is a return to a normal degree of blood destruction as measured by the fecal urobilinogen output (cf. Watson^{33b, c}) or the pigment excretion may even become lower than normal (Singer, Miller and Dameshek^{31d}). Various observers (Gripwall,¹⁴ Ham and Castle^{10b}) have on this account postulated that the spleen is the most important organ in this disease, the bone marrow simply producing abnormal red cells. The hemolysin theory^{7a, b} on the other hand states that the shape of the red cells is altered outside the bone marrow by the action of hemolysins. Spherocytosis is interpreted as a precursor of hemolysis and the morphological expression of an alteration in the structure of the erythrocyte produced by various types of hemolytic substances.

In symptomatic hemolytic anemia, we must assume from the standpoint of the hemolysin theory, that the fundamental pathological lesion either itself produces or stimulates the production of hemolysins. If the hemolysin (or agglutinin) is of the immune body type, as in our case of pneumonia, it will occasionally be demonstrated. The demonstration of other types of hemolysins in these cases has thus far not been successful. Since various lesions of the spleen may be associated with the identical picture of symptomatic hemolytic anemia, one may suspect a direct stimulation of the spleen by these abnormal tissues. On the other hand, in the cases in which the hemolytic anemia is associated with an extrasplenic lesion (dermoid cyst for example) a more indirect process of stimulation must be assumed. The hemolysin theory, although in many respects highly hypothetical, offers at least some explanation of these obscure pathological conditions and may serve as a working hypothesis for further experimental investigations.

Ham and Castle^{16b} have recently proposed another explanation for the hemolytic state, based in part on the work of Knisely²⁸ on the histology of the spleen, and in part on experimental observations with concanavalin-A, an agglutinating substance derived from the jack bean. According to these investigators, the combination of increased stasis (usually splenic) and agglutination is sufficient to explain the various types of hemolytic anemia. This explanation does not appear to have much significance in most of our cases of symptomatic hemolytic anemia, in which neither increased stasis nor agglutination (except in Case 6) were present. Recent experiments of Dameshek and Miller^{7d} have tended to cast doubt on the importance of the factor of stasis while confirming the factor of damage to the red cell envelope by both hemolysins and agglutinins. It seems likely that substances which damage the red cell envelope develop occasionally in a number of different pathological conditions, and may result in "symptomatic" hemolytic anemia. These substances may frequently be of splenic origin. The spleen is probably not only a passive, mechanical organ of stasis, as stressed by Ham and Castle, but an active, cellular organ which may produce erythrocyte-injuring substances. As the result of the recent investigations of both groups of investigators, it seems likely the hemolytic syndromes are due to various etiological mechanisms involving hemolysins, agglutinins, complement activity, mechanical trauma, and constitutionally damaged red cells. We believe that certain disorders, notably lymphatic leukemia, lymphoid neoplasms, Hodgkin's disease and some infectious states occasionally result in hemolytic anemia by evoking one or more of these mechanisms.

SUMMARY

A series of cases of acute hemolytic anemia occurring in conjunction with other diseases (dermoid cyst, chronic lymphatic leukemia, Hodgkin's disease, lymphosarcoma, severe liver disease, and pneumonia with a pan-

agglutinin) is described. These cases are classified as "symptomatic," a sub-group of the acquired hemolytic cases.

Spherocytosis and increased hypotonic fragility are often present in these cases, although a "pseudo-macrocytic" blood picture may be present. The presence of spherocytosis in these cases may indicate that this abnormality of the erythrocyte is due to certain as yet undefined hemolyzing agents.

The recognition of these cases is of distinct importance (*a*) in evaluating the type of anemia in certain cases of lymphomatous disease, and (*b*) in ruling out the presence of an "idiopathic" hemolytic process. Splenectomy may be valueless, but removal of the underlying process, such as a dermoid cyst, may be curative.

From the standpoint of pathogenesis, the recognition of these cases is further evidence in support of the hypothesis that hemolytic agents of various types, usually acting through the spleen, are responsible for the various types of hemolytic anemia. Certain disorders, notably lymphatic leukemia, lymphoid neoplasms, Hodgkin's disease, and some infectious states occasionally result in hemolytic anemia by evoking various types of etiological mechanisms.

BIBLIOGRAPHY

- 1 AUB, J. C., FAIRHALL, L. T., MINOT, A. S., and REZNIKOFF, P. Lead poisoning, *Medicine*, 1925, iv, 1.
- 2 BENNETT, W., and GOUTTAS, A. Lymphogranulomatose maligne. Terminaison par l'anémie grave, *Sang*, 1934, viii, 288.
- 3 VAN DEN BERGH, A. A. H., and KAMERLING, A. W. C. G. Un cas de cirrhose hépatique accompagnée d'anémie hémolytique et d'une hématinémie massive, *Ann d. Med.*, 1935, xxxviii, 309.
- 4 VON BRAITENBERG, H. Lymphogranulomatose mit hämolytisch anämischen Syndrom, *Frankfurt. Ztschr. f. Path.*, 1937-38, li, 515.
- 5 BRUINS SLOT, W. J. Hemolytic anemia in malignant lymphogranuloma, *Nederl. Tijdschr. v. Geneesk.*, 1938, lxxxii, 38.
- 6 CAROLI, J., and LAVERGNE, H. Ictère hémolytique aigu par carcinomatose de la moelle osseuse secondaire à un cancer de l'estomac, *Bull. et mem. Soc. med. d. hôp. de Paris*, 1937, ii, 1056.
- 7a DAMESHEK, W., and SCHWARTZ, S. O. Acute hemolytic anemia, *Medicine*, 1940, xix, 231.
- 7b DAMESHEK, W., and SCHWARTZ, S. O. Hemolysins as the cause of clinical and experimental anemia, *Am. Jr. Med. Sci.*, 1938, cxcvi, 769.
- 7c DAMESHEK, W. Target cell anemia, *Am. Jr. Med. Sci.*, 1940, cc, 445.
- 7d DAMESHEK, W., and MILLER, EDWARD B. The pathogenesis of hemolytic anemia (Unpublished data).
- 8a DAVIDSON, L. S. P., and FULLERTON, H. W. Macrocytic anemia with hemolysis in liver cirrhosis, *Quart. Jr. Med.*, 1938, vii, 43.
- 8b DAVIDSON, L. S. P. Macrocytic hemolytic anemia, *Quart. Jr. Med.*, 1932, xxv, 543.
- 9 ENGELBRETH-HOLM, J. A study of tuberculous splenomegaly and splenogenic controlling of the cell emission from the bone-marrow, *Am. Jr. Med. Sci.*, 1938, cxcv, 32.
- 10 EPPINGER, H. *Hepato-lineale Erkrankungen*, 1920, Springer, Berlin.
- 11 FELLINGER, K., and KLIMA, R. Untersuchungen ueber Anämien bei Leberzirrhosen, *Ztschr. klin. Med.*, 1934, cxxxvi, 547.

- 12 FREUND, M Hemolytic jaundice not influenced by splenectomy, *Am Jr Dis Child*, 1932, xliii, 645
- 13 GIFFIN, H Z Tuberculosis of spleen, *Med Clin N Am*, 1919, iii, 765
- 14a GRIPWALL, E Zur Klinik und Pathologie des hereditären haemolytischen Ikterus, *Acta med Scand*, 1938, supplementum xcvi
- 14b GRIPWALL, E Operierter Fall einer bei uns unbekannten Art von Splenomegalie, *Acta med Scand*, 1932, lxxix, 489
- 14c BERGQUIST, Bo and GRIPWALL, E Beiträge zur Kenntnis der Differentialdiagnose zwischen Splenogranulomatosis siderotica und Lymphogranulomatose, *Acta Path et Microbiol Scand*, 1935, xii, 79
- 15a HADEN, R L Mechanism of increased fragility of the red blood cells in congenital hemolytic jaundice, *Am Jr Med Sci*, 1934, clxxxviii, 411
- 15b HADEN, R L The nature of hemolytic anemia A Symposium, 1939, U Wisconsin Press, Madison
- 15c HADEN, R L Principles of hematology, 1939, Lea and Febiger, Philadelphia
- 15d HADEN, R L, and EVANS, F D Sickle cell anemia in the white race, *Arch Int Med*, 1937, lx, 133
- 16a HAM, T H Studies on destruction of red blood cells I Chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria, *Arch Int Med*, 1939, lxiv, 1271
- 16b HAM, T H, and CASTLE, W B Relation of increased hypotonic fragility and of erythrocytosis to the mechanism of hemolysis in certain anemias, *Proc Phil Soc*, 1940, lxxxii, 411
- 17 HARVEY, A M, and JANEWAY, C A The development of acute hemolytic anemia during administration of sulfanilamide, *Jr Am Med Assoc*, 1937, cix, 12
- 18 HEILMEYER, L, and ALBUS, L Die hamolytische Hypersplenie, *Deutsch Arch klin Med*, 1935, clxxxviii, 89
- 19 HOLLER, G, and PASCHKIS, K Abdominale Form des Lymphogranuloms, *Wien Arch inn Med*, 1927, xiv, 149
- 20 HOWELLS, L Tuberculous splenomegaly, *Brit Jr Tuberc*, 1939, xxxiii, 178
- 21 KAMINER, S, and ROHNSSTEIN, R Ueber Phenylhydrazinämie, *Berl klin Wchnschr*, 1900, xxxi, 687
- 22 KLIMA, R Hemolytische Anämie in Leukämie, *Wien Arch inn Med*, 1935, xxi, 277
- 23 KNISELY, M H Spleen studies I Microscopic observations of the circulating system of living unstimulated mammalian spleens, *Anat Rec*, 1936, lxxv, 23, II Microscopic observations of the circulating system of living traumatized spleens and of dying spleens, *ibid*, 1936, lxxv, 131
- 24 KOHN, S E Anemia during treatment with sulfanilamide, *Jr Am Med Assoc*, 1937, cix, 1005
- 25 KWASZEWSKA, G Hamolytische Anämie und Lymphogranulomatose, *Wien klin Wchnschr*, 1931, 684
- 26 MARCHAIL, G, DAVY, and GRUPPER Ictère et anémie hemolytiques avec myelome (rouge et leucémie lymphoïde a forme splénomégalique), *Sang*, 1934, viii, 852
- 27 NAFGIL, O Blutkrankheiten und Blutdiagnostik, 1931, Julius Springer, Berlin
- 28 PARKES-WEBER F, and SCHWARZ, E Severe relapsing anemia in case apparently of Hodgkin's disease, *Lancet*, 1934, i, 680
- 29 PASCHKIS, K Ueber atypische hamolytische Anämien, *Ztschr f klin Med*, 1927, cv, 301
- 30 RHODES, C P Aplastic anemia In a symposium, 1939, U Wisconsin Press, Madison
- 31 ROSENBURG, D M Macrocytic anemia in liver disease particularly cirrhosis, *Am Jr Med Sci*, 1936, cxii, 86
- 32 SCHIAPOLLI, I Granuloma malignum localized in liver and spleen with hemolytic anemia, *Minerva Med*, 1934, i, 575 Abstract in *Am Jr Cancer*, 1936, xxi, 874
- 33 SYDERHEIM, R, LEHMANN, W, and WIEHLS, P Intestinale perniziose Anaemie beim Hund durch experimentelle Dünndarmstriktur *Krankheitsforschung* 1927, iv, 263

- 34a SINGER, K The lysolecithin fragility test, *Am Jr Med Sci*, 1940, cxcix, 466
- 34b SINGER, K Das Problem der Milzhamolyse, *Wien Arch inn Med*, 1937, xxxi, 59
- 34c SINGER, K Ueber das hamolytische Syndrom als klinische Erscheinungsform des Lymphogranuloms, *Med Klin*, 1936, xxxii, 179
- 34d SINGER, K, MILLER, E B, and DAMESHEK, W Hematological changes following splenectomy, *Am Jr Med Sci*, 1941, ccli, 171
- 35 SUAREZ, C V, and ETCHIVERRI, M A A ciste dermoidea del hilio esplenico esplenomegalia icterica hemolitica y anemia grava, *Arch argent de enferm d ap digest y de la nutricion*, 1936-37, xii, 168
- 36a THOMPSON, W P Hemolytic jaundice, *Bull N Y Acad Med*, 1939, xv, 177
- 36b THOMPSON, W P Hemolytic jaundice, *Jr Am Med Assoc*, 1936, cvii, 1776
- 37 TROISIER, J and TRUFR, L Quoted by Matchall et al
- 38a WATSON, G J Hemolytic jaundice and macrocytic hemolytic anemia, *ANN INT MED*, 1939, xii, 1782
- 38b WATSON, G J Studies of urobilinogen I-III *Am Jr Clin Path*, 1936, vi, 458, *Arch Int Med*, 1937, lvi, 196, 206
- 38c WATSON, G J The pyrrol pigments with particular reference to normal and pathological hemoglobin metabolism, in *Downey's Handbook of Hematology*, 1938, Paul B Hoeber and Co, 4 Sec 35 2447
- 39 WAUGH, T R Hemolytic anemia in carcinomatosis of the bone marrow, *Am Jr Med Sci*, 1936, cxcii, 160
- 40 WEST-WATSON, N, and YOUNG C J Failed splenectomy in acholuric jaundice and the relation of toxemia to hemolytic crises, *Brit Med Jr*, 1938, i, 1305
- 41 WIDAL, F, ABRAMI, P, and BRULL, M Pluralité d'origine des ictères hemolytiques recherches cliniques et experimentales, *Bull et mem Soc med d hôp de Paris*, 1907, xxiv, 1354
- 42a WINTROBE, M M Relation of disease of liver to anemia, *Arch Int Med*, 1936, lvi, 289
- 42b WINTROBE, M M, and SHUMAKER, H S The occurrence of macrocytic anemia in disorders of the liver, *Bull Johns Hopkins Hosp*, 1933, lvi, 387
- 43 WRIGHT, D O Macrocytic anemia and hepatic cirrhosis, *Am Jr Med Sci*, 1935, clxxxix, 115

EXPERIMENTAL EXOPHTHALMOS AND ASSOCIATED MYOPATHY INDUCED BY THE THYROTROPIC HORMONE*

By ROBERT B AIRD, M D , *San Francisco, California*

THE term "malignant exophthalmos" designates the progressive and alarming proptosis which occurs in a small group, usually after thyroidectomy and in the presence of a low basal metabolic rate. Unless relieved by operative decompression of the bony orbit, as devised by Naffziger,¹ a high percentage of these patients develop corneal ulceration, infection, and fatal intracranial extension of the orbital cellulitis. The pathologic changes and immediate cause of the exophthalmos occurring in these patients were described in detail in previous reports.¹ In brief, the extraocular muscles were found to be enlarged from three to eight times. Grossly, the musculature of the orbital muscle cone was observed to be firm, pale and edematous. Various stages of degeneration were observed histologically with interstitial edema, proliferation of small round cells which tended to accumulate around blood vessels, and fibrosis which appeared more dense and extensive in the more advanced cases (figures 1, 2 and 3).

The fact that exophthalmos may occur with hyperthyroidism and yet may steadily progress to a malignant form in the presence of postoperative hypothyroidism suggests an indirect relationship with hormones affecting the thyroid gland, such as the thyrotropic hormone of the anterior pituitary body. A review of all cases of malignant exophthalmos in the University of California Hospital strongly suggested a glandular dysfunction in the majority of these patients, and in many instances the findings were consistent with some disturbance of the hypophysis. Because of the successes recently reported in the experimental production of exophthalmos by the use of whole extracts of the anterior pituitary body, the present studies were centered about this method.

A historical review of the older research and theories on exophthalmos,¹ as well as its experimental production with the use of extracts of the anterior pituitary body,² has been presented in detail previously and need not be repeated.

Although pathologic changes in the muscles were described in certain of these studies in which exophthalmos was produced experimentally by means of injections of the extracts of the anterior pituitary body,³ it is by no means clear that the changes were primarily those of a myopathy, as is the case in the malignant exophthalmos of human beings. Furthermore, although the

* Received for publication March 27, 1941.

From the Department of Surgery, University of California Medical School.

This work was conducted under grants from the Christine Bron Fund for Medical Research.

thyrotropic hormone in the extracts of the anterior lobe of the pituitary body was suspected as the factor responsible for the production of exophthalmos, conclusive evidence has not been obtained to substantiate this impression. The following experiments were undertaken to clarify these points.

METHODS

The extracts of the anterior pituitary body used in these studies were

- 1 An alkaline extract of the whole pituitary body as prepared by Parke, Davis and Co.*
- 2 An alkaline extract of the whole pituitary body as prepared by E. R. Squibb and Sons.*
- 3 A thyrotropic extract prepared according to the method of Junkmann, by Uyei† of the Institute of Experimental Biology of the University of California.
- 4 An adrenotropic extract prepared by Moon† according to the method described by Lyons.

Injections were made by the intraperitoneal route except in the case of the Junkmann preparation which was used subcutaneously. All injections were given daily over periods of from three and one-half to seven months, as indicated in each case.

Young male guinea pigs weighing between 200 and 400 grams were used in all tests. The animals were maintained on a diet of alfalfa and barley, with the addition of carrots once a week. Cauliflower leaves were substituted for this diet one day a week. The guinea pigs were weighed every two weeks, and measurements of their eyes were recorded weekly. Objective measurements of the eyes proved difficult. Direct methods were impractical, as they frightened the animals and resulted in struggling and sympathetic hyperactivity. Photographic methods were attempted, but the bright lights, essential for obtaining good pictures under identical lighting conditions, tended to make the guinea pigs close their eyes. The method that finally proved satisfactory was an optical system which utilized the principle of the camera lucida and, without disturbance to the animal, permitted indirect tracings of the eyes to be made quickly and accurately from a superior angle. The details of this method have been described previously.²

At the conclusion of each experiment the eyes and muscle cones of all guinea pigs were carefully dissected from the orbits, and the retrobulbar fat and tissues were examined. The eyeballs were measured and the extraocular muscles were fixed in a 10 per cent solution of formalin. Except in the initial group, in which the Parke, Davis preparation was used, each extraocular muscle was studied by two methods. One portion was stained by the

* Acknowledgment is made to Parke, Davis and Co. and E. R. Squibb and Sons for the extracts used in these studies.

† Drs. Uyei, Moon and Evans of the Institute of Experimental Biology of the University of California cooperated in preparing these extracts.

routine hematoxylin and eosin technic, the method used in the initial experiment referred to above, and the second by the Bodian method⁴ for the nerve endings and the motor end-organs. The Bodian method also showed the muscle structure to good advantage and served as a check upon the hematoxylin and eosin preparations. In addition, specimens were taken from the right deltoid muscle of each pig as a control on the possibility that myopathy might have occurred elsewhere. These specimens were fixed in a 10 per

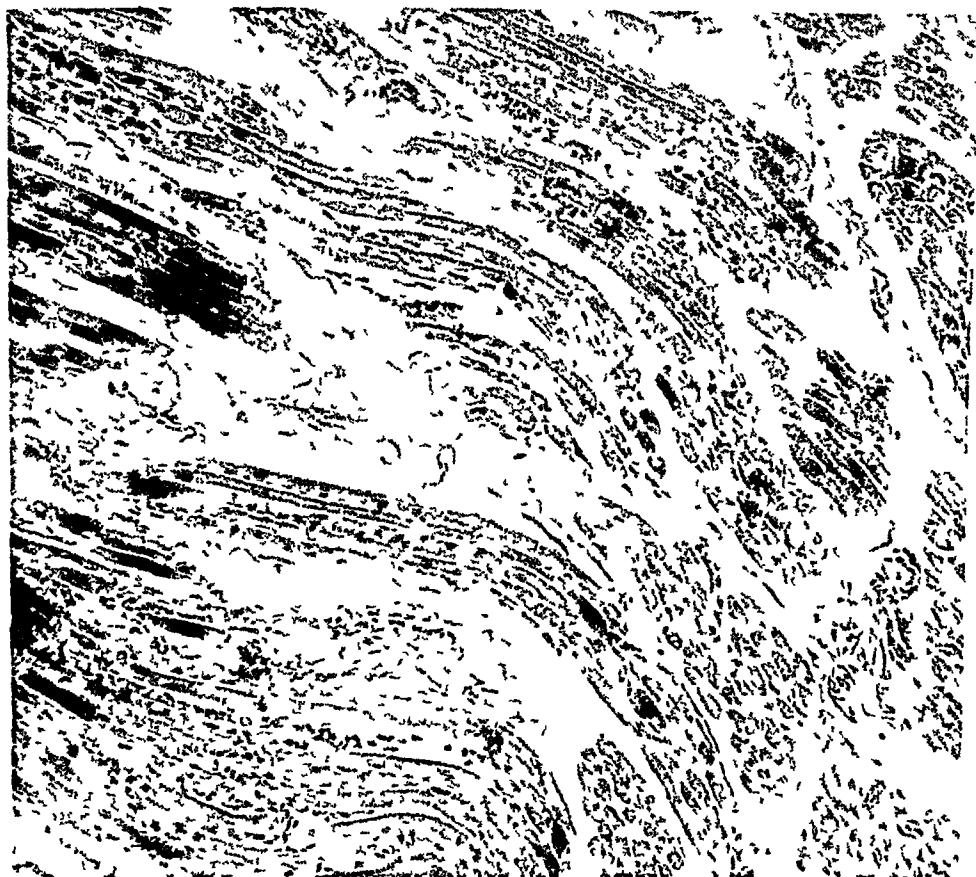


FIG. 1 Normal extra-ocular muscle of human being H and E ($\times 105$)

cent solution of formalin and were prepared for study by the usual hematoxylin and eosin staining technic.

In the initial experiment (Parke, Davis preparation) the thyroid glands were fixed in Zenker's solution and stained with hematoxylin and eosin. In the other experiments the pituitary, thyroid, and adrenal glands and the testes were removed from each animal, their sizes recorded, and sections of each fixed in Zenker's solution. In the final two experiments (adrenotropic and thyroidectomized control groups) the pituitary bodies were fixed in Flemming's solution and specially stained by Koneff of the Department of Anatomy of the University of California. The other glands were stained with hematoxylin and eosin. In addition, the adrenal glands were stained with Sudan IV and, in many instances, counterstained with methylene blue to determine the degree of lipid depletion present in each gland.

The kidneys of each animal were measured as a control on the variations of size normally occurring in individual organs. Sections of the kidney and liver were fixed in Zenker's solution, stained by routine hematoxylin and eosin methods, and studied for evidence of changes suggesting toxic effects.



FIG 2 Myopathy of moderate degree in patient afflicted with malignant exophthalmos showing the interstitial edema and perivascular infiltration of small round cells. H and E ($\times 105$)

RESULTS

I Experimental exophthalmos produced by the whole extract of the anterior lobe of the pituitary body—Parke, Davis and Co preparation Eight of 12 male guinea pigs weighing approximately 400 grams each were injected daily by the peritoneal route with 1 c.c. of the alkaline extract of the whole pituitary body prepared by Parke, Davis and Co. The injections were continued over a period of seven months. Five guinea pigs of the group injected and the four controls survived the duration of the experiment.

In the animals injected a slight but definite exophthalmos appeared in approximately six weeks and slowly progressed throughout the period of administration of the extract. One or both eyes of all these guinea pigs became exophthalmic. The measurements of the eyes varied from 3.5 to 5 mm. as compared to a maximum reading of 3 mm. in the control group.

Toward the end of the experiment the average measurement in the control was slightly over 2.5 mm. Control studies indicated the method to be accurate to within 0.5 mm. Although the measurable exophthalmos was only from 0.5 to 2 mm, the constancy of these measurements and the accuracy of the methods made it certain that the phenomenon observed was real. Considering the incomplete bony orbits of guinea pigs and the size of these animals, it is evident that the changes were, in a relative sense, striking.

Except for one pig, whose exophthalmos was perhaps the greatest and most consistent throughout the whole period of injections, the weights of the



FIG 3 Advanced myopathy in patient with malignant exophthalmos showing edema, the infiltration of small round cells, degenerative changes in the muscle fibers and fibrosis H and E ($\times 105$)

injected and control pigs were roughly comparable. The weight of the exceptional pig was under that of the others throughout the experiment and at the end was 780 grams as opposed to an average weight of 980 grams. The other guinea pigs varied in weight only 80 grams.

At the end of the seven months three guinea pigs of the injected group and two controls were killed and measurements of the eyes after death were recorded. Although their eyes were less prominent than during life, those of the injected animals were still from 1 to 1.5 mm more prominent than those of the controls. The remaining two exophthalmic pigs and the controls were observed for another month, during which period no injections were given. The exophthalmos receded slightly in one guinea pig, in the other animal one eye (not exophthalmic) remained the same and the exophthalmos in the other eye was slightly accentuated. At the end of the eighth

month the postmortem measurements on the eyes of these guinea pigs likewise exceeded those of the controls. In this same connection it had been observed that ether anesthesia, although appreciably diminishing the exophthalmos, by no means abolished it.

The extraocular muscles of this group proved to be of interest. Grossly they appeared slightly larger in the animals injected than in the controls. Upon microscopic study the extraocular muscles of the injected guinea pigs



FIG 4 Normal extra-ocular muscle of guinea pigs H and E ($\times 120$)

showed slight degenerative changes with interstitial edema, characterized by some loss of cross striations, an increased number of nuclei, which were smaller and more deeply stained than those of the controls, a tendency toward the separation of muscle fibers associated with poor alignment and suggestive breaking up of the fibers, and, finally, an increase in cellular debris. In addition, a process of cellular infiltration was observed, mostly of small round cells in clusters or "nests," but also of occasional polymorphonuclear cells. A wider variation in the size of the fibers was noted in the injected animals than was seen in the controls, and in those injected there was a tendency to the formation of giant fibers. The staining in the first group was correspondingly more irregular and unequal (figures 4 and 5).

The retrobulbar fat and tissues did not appear unusual in the injected animals. Slight edema of these tissues, as well as of the lacrimal glands, was observed occasionally, but this finding was not consistent nor did it correlate with the measured exophthalmos. The eyeballs were of the same size in both groups.

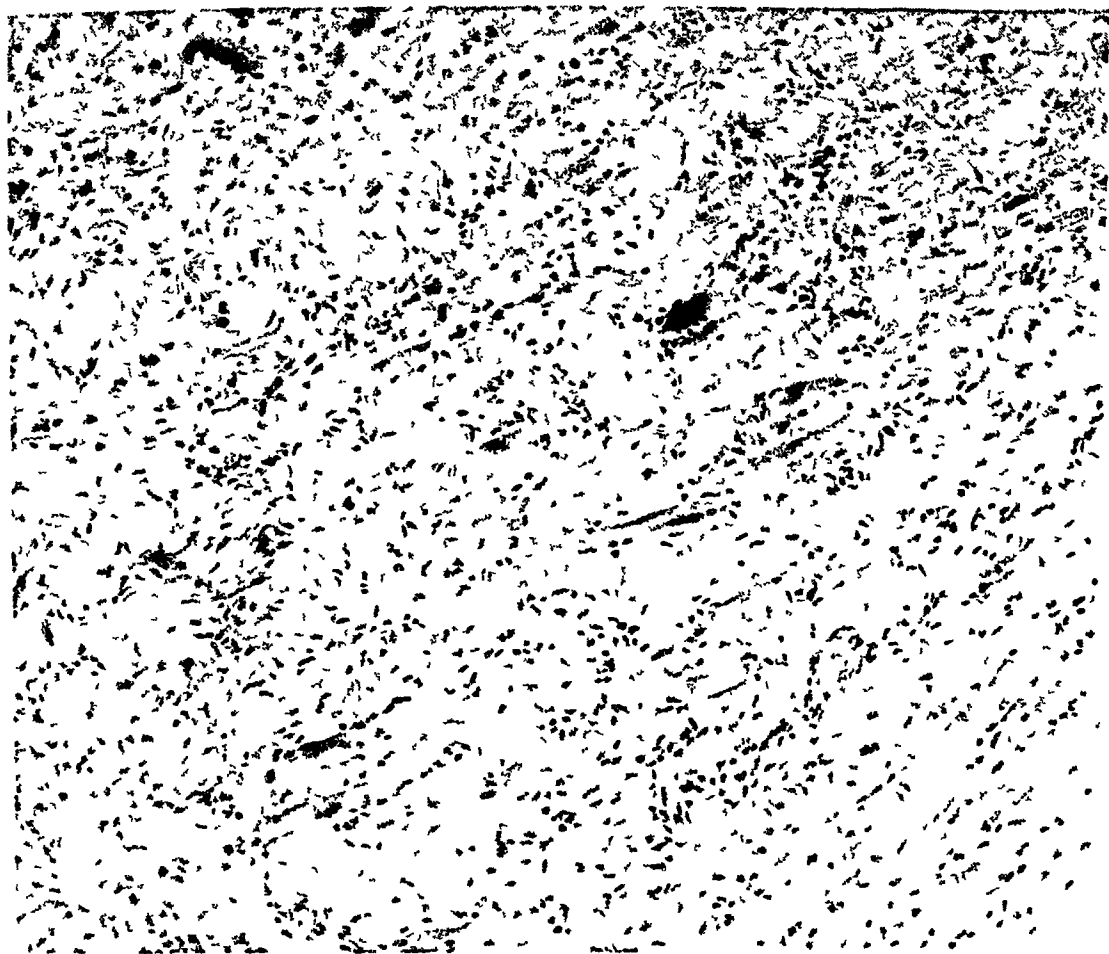


FIG. 5. Myopathy of moderate degree in the extra-ocular muscles of the guinea pig treated with the whole extract of the anterior lobe of the pituitary body. Note the cellular infiltration and the unequal staining, loss of cross-striation and poor alignment of the muscle fibers. H and E ($\times 120$).

Although occasional thyroid glands of the injected guinea pigs showed changes compatible with a hypothyroid state of mild degree, in general these glands appeared to be within the limits of normal, as judged by the microscopic appearance of those of the control animals.

II. Experimental exophthalmos produced by the whole extract of the anterior pituitary body—E. R. Squibb and Sons preparation. Thirteen of 17 guinea pigs were given daily injections intraperitoneally of 0.5 cc of the alkaline extract of the whole pituitary body prepared by E. R. Squibb and Sons. Young male guinea pigs weighing between 250 and 350 grams were used. Their diet, care and follow-up studies were as previously indicated.

under Methods The outstanding feature in this experimental group, aside from the development of exophthalmos, was the curious clinical course. They underwent a severe reaction which, because of the manifestations of restlessness, hyperactivity, loss of weight and gross enlargement of the thyroid glands as seen at autopsy among those succumbing, was interpreted as having been caused by acute thyrotoxicosis. Of the 13 guinea pigs receiving injections, seven died between the ninth and twelfth days. One other died on the thirty-fifth day of injection. The condition of the five surviving guinea pigs of the test group gradually changed from an acute thyrotoxicosis to a normal or even slightly hypothyroid state. They became more quiet and put on weight slightly in excess of that occurring in the control group. These changes continued throughout the period of injection. Coincidental with the establishment of this refractory state, that is, from four to six weeks after the injections were begun, these animals showed objective evidence of exophthalmos in one or both eyes. The injections were continued over a period of five months, in three instances, and six months in the other two guinea pigs. The exophthalmos slowly progressed and, in most instances, tended to reach a peak at approximately the second month and again at the fifth. In one animal a gradual progression occurred through the entire five months and in another a plateau, attained by the third month, was exceeded only slightly at the end of six months of injections. If a maximum of 3 mm is set for a normal reading (the average was 2.5 mm in the control group), exophthalmos of from 0.5 to 1.5 mm, by measurement, occurred bilaterally in all of the guinea pigs injected. In seven of the 10 eyes the measurements were 4 mm or more toward the end of the experiment. Although slight, the exophthalmos was within the limits of accuracy of the objective method used for measuring it, and the constancy of the results left no doubt as to the existence of this phenomenon.

Grossly the retrobulbar fat and tissues appeared to be within the limits of normal in this group, and the eyeballs of both injected and control animals were of the same size. As in the first experimental group, slight edema was noted in the retrobulbar tissues and lacrimal glands of occasional guinea pigs, but this observation was also made in one of the controls, and in general could not be correlated with the measured exophthalmos.

The microscopic appearance of the extraocular muscles was essentially the same as in the previous group (in which the Parke, Davis preparation was used), except that the picture was less well defined, the pseudohypertrophy was less apparent, the nuclei were fewer and paler, and the cellular infiltration was more questionable. The nerve endings and end-organs appeared to be normal.

Although at the beginning of the experiment the average weight of the guinea pigs in the control group slightly exceeded that of those to be injected, the reverse was true at the end. The difference in average weight was slight, however, and probably not significant. The adrenals, testes and

III. *Experimental exophthalmos produced by the thyrotropic factor (Junkmann preparation) of the anterior pituitary body* Eleven of 15 young male guinea pigs weighing between 250 and 350 grams were given daily subcutaneous injections of 0.2 cc. of a 2 per cent solution of the thyrotropic hormone prepared by Uyer of the Institute of Experimental Biology of the University of California, according to the Junkmann method. The adjustment of the pH of the solution to 7.5-8 by the addition of a few drops of sodium hydroxide solution greatly facilitated the preparation of the solution used for injection. By biological assay 5 mg. of this solution was found to possess the potency of 100 thyrotropic units. The daily subcutaneous dose was therefore 80 thyrotropic units.

The course of the animals injected was of considerable interest in that it paralleled that of the group which received the alkaline extract of the whole anterior pituitary body supplied by E. R. Squibb and Sons. The test guinea pigs underwent a severe reaction which, because of its manifestations of restlessness, hyperactivity, loss of weight and gross enlargement of the thyroid gland seen at autopsy among those succumbing, was interpreted as an acute thyrotoxicosis. Of the 11 guinea pigs receiving injections three died on the eleventh or twelfth day and four others within a month. Three of the seven guinea pigs that died had one or both eyes clawed out. Four guinea pigs survived this stage and from an acute thyrotoxicosis gradually shifted to a condition characterized by signs directly the reverse of those described for the toxic state. They became quiet, tractable, and gained weight slightly in excess of that occurring in the control group. The average weight of the four surviving guinea pigs after five months of injection was 623 grams as compared with an average weight of 539 grams for the four

controls at the same time. This change is all the more striking because, initially, the control animals were, on the average, slightly heavier than the test group. These changes, interpreted as being hypothyroid in character, continued in spite of the daily injections of thyrotropic extract. Coincidentally with the onset of this hypothyroid state, that is, from four to six weeks after the injections were begun, these animals first showed evidence of exophthalmos. Injections were continued over a period of four or five months, when it was felt that the functional changes would have had time to project themselves in some permanent pathological pattern. The exophthalmos slowly progressed throughout this period and at the end the changes were so marked as to permit correct selection of the injected guinea pigs by casual inspection. By measurement the exophthalmos varied from 1 to 2.5 mm in comparison with the eyes of the control animals. This group showed exophthalmos more consistently and to a more marked degree than either of the previous groups which received injections of the alkaline extracts of the whole anterior pituitary body. Correspondingly, the microscopic changes in the extraocular muscles of this group were the most marked, the cellular infiltration and the appearance of giant fibers being most accentuated (figures 6 and 7). The nerve endings and motor end plates appeared to be normal. The retrobulbar fat and tissues and the lacrimal glands of occasional guinea pigs appeared to be edematous, but, as in the earlier groups, this finding was not consistent and could not be correlated with the measured exophthalmos.

The study of the glands in this experiment proved of interest. Grossly the thyroids, testicles and adrenals of the injected animals were considerably enlarged over those of the controls. The difference was more than could be explained on the basis of the general slight increase in size of the injected guinea pigs. The average difference in weight was only 14 per cent, but the adrenal glands of the injected group were, on the average, over 50 per cent larger than those of the control animals, while the thyroids and testicles of the injected animals were 40 per cent and 17 per cent, respectively, larger than those of the controls. These findings were borne out in the microscopic studies.

The thyroids of the injected animals possessed large acini, which were filled with dense colloid, and, along with the abundant stroma, gave the appearance of a mild myxedema in comparison with the controls.

The adrenal cortex was thickened and the enlarged cells definitely showed evidence of hyperplasia. The fat was increased throughout the cortex, and a diffuse hyperemia was present. These changes indicated a considerable degree of adrenal cortical stimulation. This seems best explained on the basis of the appreciable amount of adrenotropic hormone known to be present in the Junkmann preparation. Biological assay of this preparation by Moon⁵ had shown about 1 unit (20 mg.) of adrenotropic hormone in from 100 to 120 mg. of the Junkmann preparation. Thus a dose of 4 mg. of this preparation, as was used daily in this study, contained from 0.7 to 0.8 mg.



FIG. 6. More advanced myopathy in experimental exophthalmos. The guinea pigs were treated over prolonged periods with the human preparation of the thyrotropic hormone. The marked cellular infiltration which is largely perivascular is well illustrated, as is the loss of cross-striation and separation of muscle fibers. (H and E $\times 250$).

of adrenotropic hormone or approximately one twenty-fifth of a unit. Since doses considerably less than 1 unit are known to be effective, it seems entirely possible that daily doses of one twenty-fifth of a unit might eventually produce very appreciable effects, such as the adrenocortical changes observed.

The convoluted tubules of the testes showed hyperplastic changes and the lumens were occluded with debris and secretion. The pituitary bodies were not unusual, and the deltoid muscle, liver and kidneys appeared to be normal in all animals.

IV Control experiment to test the possible relationship between exophthalmos and hypothyroidism (thyroidectomized controls) Eleven of 15 guinea pigs weighing between 230 and 370 grams were thyroidectomized. Their weights and the measurements of their eyes were observed over a six months' course in a manner similar to that outlined under Methods. They received no injections, the object of this experiment being to rule out hypothyroidism itself as an etiological factor in the production of exophthalmos. Such a relationship was suggested by the fact that the onset of



FIG 7 Myopathy of the extra-ocular muscles of guinea pigs treated with the Junkmann preparation of the thyrotropic hormone, showing the cellular infiltration and unequal staining, loss of cross-striation and separation of the muscle fibers H and E ($\times 250$)

exophthalmos occurred in two of the previous groups in what was interpreted as a refractory state of hypothyroidism in those guinea pigs surviving the initial period of acute thyrotoxicosis

Nine of the 11 thyroidectomized guinea pigs survived four months or longer, and of the 18 eyes observed over this period only one suggested any appreciable degree of exophthalmos. This was not borne out, however, in the pathological studies, which showed all the eye muscles to be within the limits of normal. The retrobulbar tissues likewise were found to be normal. Careful search for remaining tags of thyroid tissue was made at the time of the autopsy in all nine thyroidectomized guinea pigs. Single, small, round pieces of thyroid tissue, 0.2 mm in diameter, were found in three animals. On microscopic examination these bits of tissue showed hyperplastic changes.

The differences in size between the thyroidectomized and control animals at the beginning and end of the experiment, and the differences in size of the organs of both groups were not significant. The adrenals, testes, kidneys, livers and right deltoid muscles appeared normal to microscopic study.

V Control experiment to test the possible relationship between exophthalmos and the adrenotropic factor of the anterior pituitary body In the experiments in which exophthalmos was successfully produced, appreciable and effective amounts of adrenotropic hormone were known to be present in the extracts injected. Hypertrophy and hyperplastic changes of the adrenal cortex also occurred. Such changes have been described previously, associated with hyperactivity of this organ. Since adrenocortical hormones are known to play a fundamental rôle in the reactivity of muscle and in metabolism,⁶ the possibility of a relationship between these hormones and exophthalmos must be considered. The following experiment was performed to test the possibility of an etiological relationship between exophthalmos and either the direct effect of the adrenotropic hormone on the pituitary body or the indirect effect of adrenocortical hormones elaborated in response to the stimulatory effects of the adrenotropic hormone.

Using the same technic as for the previous groups, eight of 12 male guinea pigs were given daily intraperitoneal injections of 0.5 cc of 1 per cent solution of adrenotropic hormone prepared for this study by Moon according to the method described by Lyons.⁷ Biological assay showed a potency of one adrenotropic unit per 20 mg of the powdered preparation, so that the daily dose was estimated to be one-fourth of one unit. Ten other similar preparations of adrenotropic hormone, made and tested by Moon,⁸ had failed to show evidence of any thyrotropic hormone. A dose of 100 mg showed no evidence of stimulation of the thyroid in the squab, although 0.1 mg of thyrotropic hormone (that is, one part in a thousand of the total dose given) produced a recognizable stimulatory response of the thyroid in this experimental animal. Thus, in the doses used in this experiment, any thyrotropic effect other than that which might be caused by the thyrotropic hormone elaborated by the guinea pig's own anterior pituitary body can safely be ruled out. Although an indirect stimulation of the hypophysis might conceivably be caused by sex hormones formed in excess as a result of the stimulatory effect of androgenic substances (elaborated in turn by the hyperactivity of the adrenal cortex as produced in this experiment), no evidence of the excessive production of thyrotropic hormone, as judged by a study of the thyroid glands, was actually observed in this experiment. Whereas in the previous (thyrotropic) experiment there was a great excess of the thyrotropic hormone in the presence of a slight excess of adrenotropic hormone, in this experiment the reverse was true. Consequently, the failure of the production of any definite exophthalmos in this experiment, as opposed to the exophthalmos observed in the thyrotropic experiment, clearly indicates that the thyrotropic hormone alone was responsible for the production of the exophthalmos.

As might be expected under these circumstances, microscopic study showed the retrobulbar tissues to be normal and the extraocular muscles also were interpreted as being within normal limits. Likewise, the nerve endings and end-organs of the eye muscles showed no changes, nor did other

striated muscles, as judged by the histological appearance of the right deltoid muscle

It is of interest to note that a retardation of somatic growth, known to result from large doses of adrenotropic hormone,⁸ was observed in this experiment, as was gross hypertrophy of the adrenal gland. Although initially the average weight of the injected guinea pigs was 29 grams more than that of the control group, a reverse relationship had occurred toward the end of the experiment, the average weight of the injected pigs being 136 grams less than that of the control animals. Correspondingly, the thyroids, testicles and kidneys of the control group were larger than those of the injected group. The adrenals, however, were grossly 50 per cent larger in the animals which had received the adrenotropic injections. Microscopic study of these glands, stained as previously described with Sudan IV and counterstained with methylene blue, showed the characteristic changes caused by stimulation, namely, hypertrophy and hyperplasia of the cortical cells, an increase in the fat content throughout the adrenal cortex, including the normally fat-free zone intermediate between the glomerulosa and fasciculata, and diffuse hyperemia. The convoluted tubules of the testicles showed slight hyperplastic changes with occlusion of the lumina, in most instances, with cellular debris and secretion.

As already mentioned, no definite evidence of stimulation of the thyroid was observed, the acini appearing within the limits of normal and without evidence of hyperplastic changes. The livers and kidneys were normal. The pituitary bodies are being specially stained and studied by Koneff of the Department of Anatomy of the University of California, and the results are not yet available.

DISCUSSION

The interrelationship of the ductless glands renders an investigation which involves the use of the extracts of these glands a most complex problem. As a result of studies on exophthalmos in rabbits, Marine⁹ suggested that thyroid insufficiency and gonadal and androgenic activity, as well as activity of the anterior pituitary, are factors of importance in the production of exophthalmos. It is conceivable that some such pattern of glandular dysfunction is attained when any member of the chain of glands is altered in sufficient degree and manner, and that such changes may result directly or indirectly in the production of exophthalmos. The fact that the thyrotropic hormone may stimulate the thyroid to exhaustion, as was suggested in the studies in which the Squibb preparation and thyrotropic hormone, respectively, were used, would appear to be compatible with this conception. Hypertrophy and hyperplasia of the adrenal cortex were likewise observed in these studies, as was hypertrophy of the gonads in the study utilizing the thyrotropic hormone. The adrenocortical changes, however, may be adequately explained on the basis of the adrenotropic hormone known to be present in appreciable amounts in the extracts used in these experiments.

The gonadal hypertrophy likewise seems best explained on the basis of androgenic hormones resulting from the stimulatory effects of the adrenotropic hormone on the adrenal cortex, as already explained. The control study, in which a potent adrenotropic preparation free from thyrotropic hormone was used, affords strong evidence in support of these points and further suggests that exophthalmos will not necessarily result from changes effected through certain members of the closely related ductless glands. Likewise, hypothyroidism, although known to produce hypertrophy of the anterior lobe of the pituitary body, does not appear to be adequate in itself to produce exophthalmos. This possibility would seem to be ruled out by the control experiment, in which it was found that simple thyroidectomy did not result in exophthalmos. Exophthalmos following thyroidectomy has been reported,¹⁰ but its occasional incidence in slight degree is no more than has been observed in numerous other conditions, both experimentally and in human beings. Alone it does not appear to explain the frequency and intensity of the exophthalmos produced in these experiments.

An etiological relationship between exophthalmos and the gonadotropic factor of the anterior pituitary body seems to have been ruled out by the fact that the gonadotropic factor was not present in significant amounts in the thyrotropic preparation. The testicular hypertrophy in this experiment was caused by the androgenic substance elaborated in the adrenal cortex which was stimulated in turn by the adrenotropic hormone known to be present in the thyrotropic preparation. The successful production of exophthalmos in the experiment in which the Squibb extract was used and in which no testicular hypertrophy was noted, tends to substantiate this conclusion. On the other hand, this by no means rules out the activity of the interstitial cells of the gonads as a possible and necessary link in the production of exophthalmos, as suggested by the studies of Marine.¹¹

The growth hormone would appear to be ruled out as an etiological factor in the production of exophthalmos by the fact that proptosis was produced in the original experiment (in which the Parke, Davis preparation was used), in spite of the fact that there was no appreciable increase of weight or size of the injected guinea pigs over their controls. In fact, the guinea pig exhibiting the most marked and consistent exophthalmos in this experiment was notably the smallest and the slowest in development. Also, in the experiment in which the Squibb preparation was used, the increase in weight of the injected animals over their controls was relatively slight (only 5 per cent), and is probably explained on the basis of a mild myxedema. The mammotropic hormone, likewise, can be ruled out, inasmuch as it was not present in significant amounts in the thyrotropic (Junkmann) preparation.

The etiological rôle of the thyrotropic factor in the production of exophthalmos is supported not only by this negative evidence, but by the fact that the most marked exophthalmos was produced by the thyrotropic preparation, in which the dose of thyrotropic hormone was in considerable excess of that given in preparations of whole gland, while other hormones were either eliminated or markedly reduced in relative dosage.

Although the chain of physiological events essential to the production of exophthalmos is not shown by these studies, certain possibilities appear to be ruled out and support is lent to others.

Smelser²⁷ and Paulson^{28, 29} reported changes in the lacrimal glands in their experiments on exophthalmos and, in fact, tended to explain the exophthalmos in part on this basis. Paulson, however, did not report the same changes as Smelser, and those he found occurred to a less extent in his more prolonged experiments. Although changes in the lacrimal glands suggestive of those described by Paulson were occasionally observed in the present studies, the lacrimal glands of the injected group were, in general, both grossly and microscopically indistinguishable from those of the controls. These facts suggest that Paulson observed changes which tended to retrogress after approximately the first three weeks of injection and which returned essentially to normal in the present studies of much longer duration. This course of events is similar to and concurrent with the changes occurring in the thyroid gland, as found by Friedgood¹² and corroborated in the present studies. The persistence and actual progression (in an irregular manner) of exophthalmos over long periods indicates that it probably cannot be explained by changes in the lacrimal glands. Likewise, changes in other retrobulbar tissues were not found to explain the development of exophthalmos. The slight edema occasionally observed in the lacrimal glands and retrobulbar tissues showed no correlation with the measured exophthalmos. The muscle changes recently reported by Paulson³⁰ in more prolonged studies are suggestive of the changes observed in this study. His report of maximal proptosis in non-thyroidectomized guinea pigs prior to 10 days of treatment and his explanation of the exophthalmos in terms of retrobulbar edema are at variance with our observations. The shorter duration of his experiments may explain this difference.

In a comparative study of experimental and clinical exophthalmos, Smelser¹³ examined the extraocular muscle of six patients with exophthalmos. Although the clinical data for these patients are not presented, enlarged extraocular muscles were found in only two of them, and it is not clear that even these could be classified properly as examples of malignant exophthalmos. His experimental studies, in which guinea pigs were injected with the whole extracts of the anterior lobe of the pituitary body, showed edematous changes of the retrobulbar tissues, especially of the orbital fat, the dorsal lacrimal glands and, to a less extent, the extraocular muscles. Histologically, the extraocular muscles were considered to be normal. The discrepancy between these observations and the present studies, again, would seem to be best explained on the basis of the shorter duration of his experiments.

The evidence thus suggests that the early changes are chiefly edematous in character,^{3, 13} while, with continued treatment over prolonged periods, degenerative and pseudo-hypertrophic changes occur. The early edematous changes correspond to the findings described in cases of Graves' disease,¹⁴ while the late degenerative changes, as observed in the present studies, cor-

respond more nearly to a pre-fibrotic stage of the myopathy found in cases of malignant exophthalmos¹

The changes found in the eye muscles appear from these studies to be of primary importance. These changes, although relatively slight in comparison with the advanced changes observed late in human patients, seem to be consistent with the lesser degree of exophthalmos obtained in these experiments. Furthermore, the changes in the muscles of the experimental animals appear essentially similar to those found in human beings. It is also of interest that the production and maintenance of exophthalmos over long periods of time result in permanent changes which, contrary to earlier reports based upon short-term experiments, persist during narcosis and after death. The evidence is thus very suggestive that the changes experimentally produced in the extraocular muscles of guinea pigs, by means of the thyrotropic hormone of the anterior lobe of the pituitary body, are essentially the same as those observed in the extraocular muscles of human patients suffering from malignant exophthalmos.

A trial of deep roentgen-ray therapy over the pituitary body in early cases of malignant exophthalmos would be of interest. Indeed, such treatment has already been suggested and favorable results have been reported by Thomas and Woods, Ruedemann and Ginsburg¹⁵. Only in this way can critical evidence be obtained as to the common etiological relationship between the exophthalmos experimentally produced by administration of the thyrotropic hormone of the anterior pituitary body and the malignant exophthalmos of human beings. Such treatment should be limited to bona fide cases of malignant exophthalmos in which the condition is progressing. It is also suggested by the results of these studies that treatment should be instituted relatively early in the course of the disease. Satisfactory therapeutic results cannot be expected in late cases in which the changes in the eye muscles have progressed to an advanced and irreversible stage.

SUMMARY AND CONCLUSIONS

1 The exophthalmos experimentally produced by injections of the extracts of the anterior pituitary body was caused by the thyrotropic fraction. Ocular proptosis developed in the refractory period following an acute thyrotoxicosis produced by the action of the thyrotropic hormone on the thyroid gland and progressed slowly in an irregular manner. After several months of injection, the exophthalmos was found to persist in spite of the discontinuance of injections, narcosis or death.

2 Myopathy of the extraocular muscles was observed in the injected guinea pigs which developed exophthalmos. This change was sufficient to account for the degree of exophthalmos observed, as well as its permanence following prolonged treatment. Other satisfactory explanations for the exophthalmos were not found. Qualitatively, the experimental myopathy was consistent with the changes found in the extraocular muscles of human patients afflicted with malignant exophthalmos.

REFERENCES

- 1 (a) NAFFZIGER, H C Progressive exophthalmos following thyroidectomy, its pathology and treatment, *Ann Surg*, 1931, *xciv*, 582-586
 (b) NAFFZIGER, H C, and JOHNS, O W, JR The surgical treatment of progressive exophthalmos following thyroidectomy, *Jt Am Med Assoc*, 1932, *xciv*, 638-642
 (c) NAFFZIGER, H C Pathologic changes in the orbit in progressive exophthalmos, *Arch Ophth*, 1933, *iv*, 1-11
 (d) NAFFZIGER, H C Progressive exophthalmos associated with disorders of the thyroid gland, *Ann Surg*, 1938, *cvi*, 529-544
- 2 AIRD, R B Experimental exophthalmos and the associated myopathy induced by the thyrotropic hormone, *Arch Ophth*, 1940, *xviii*, 1167-1174
- 3 (a) SMELSER, G K Experimental production of exophthalmos resembling that found in Graves' disease, *Proc Soc Exper Biol and Med*, 1936, *xxxv*, 128-130
 (b) PAULSON, D L Experimental exophthalmos in the guinea pig, *Proc Soc Exper Biol and Med*, 1937, *xxxvi*, 604-605
 (c) PAULSON, D L Experimental exophthalmos and muscle degeneration induced by thyrotropic hormone, *Proc Staff Meet Mayo Clin*, 1939, *xiv*, 828-832
- 4 BODIAN, D New method for staining nerve fibers and nerve endings in mounted paraffin sections, *Anat Rec*, 1936, *lxv*, 89-97
- 5 MOON, H D Personal Communication
- 6 (a) INGLE, D J Work capacity of the adrenalectomized rat treated with cortin, *Am Jr Physiol*, 1936, *cxi*, 622-625
 (b) TIPTON, S R The effect of cortin on the electrolyte changes in cat muscle during stimulation and recovery, *Am Jr Physiol*, 1938, *cxxiv*, 322-327
- 7 LYONS, W R Preparation and assay of mammotropic hormone, *Proc Soc Exper Biol and Med*, 1937, *xxxv*, 645-648
- 8 MOON, H Inhibition of somatic growth in castrate rats with pituitary extracts, *Proc Soc Exper Biol and Med*, 1937, *xxxvii*, 34-37
- 9 MARINE, D Effect of androgens on exophthalmos in rabbits, *Proc Soc Exper Biol and Med*, 1938, *xxxviii*, 353
- 10 GLEY, E De l'exophtalmie consecutive a la thyroidectomie Presentation d'animaux, *Compt rend Soc biol*, 1910, *lxviii*, 858-862
- 11 (a) MARINE, D, and ROSEN, S H Influence of gonads on exophthalmos in rabbits, *Proc Soc Exper Biol and Med*, 1936, *xxxv*, 354-356
 (b) MARINE, D, and ROSEN, S H Effects of cryptorchidism and castration on exophthalmos in rabbits and guinea pigs, *Am Jr Physiol*, 1938, *cxxi*, 620-624
 (c) MARINE, D Studies on the pathological physiology of the exophthalmos of Graves' disease, *ANN INT MED*, 1938, *xii*, 443-453
- 12 FRIEDGOOD, H B Experimental exophthalmos and hyperthyroidism in guinea pigs, *Bull Johns Hopkins Hosp*, 1934, *liv*, 48-74
- 13 SMELSER, G K A comparative study of experimental and clinical exophthalmos, *Am Jr Ophth*, 1937, *xx*, 1189-1203
- 14 (a) MOORE, R F A note on the exophthalmos and limitations of the eye movements of Graves' disease, *Lancet*, 1920, *ii*, 701
 (b) BURCH, F E The exophthalmos of Graves' disease, *Minnesota Med*, 1929, *xii*, 668-675
- 15 (a) THOMAS, H M, JR, and WOODS, A C Progressive exophthalmos following thyroidectomy, *Bull Johns Hopkins Hosp*, 1936, *lix*, 99-113
 (b) RUEDEMANN, A D Exophthalmos, *Cleveland Clin Quart*, 1937, *iv*, 66-75
 (c) GINSBURG, S Postoperative progressive exophthalmos with low basal metabolic rate, *ANN INT MED*, 1939, *xiii*, 424-450

THE RESPONSIBILITY OF THE AMERICAN COLLEGE OF PHYSICIANS FOR POSTGRADUATE TRAINING¹

By EDWARD L. BORTZ, F A C P, *Philadelphia, Pennsylvania*

THE activities of the American College of Physicians are in accord with the principle that a progressive medical policy on a national scale requires a program of continuous education for the doctors of the nation

As stated in the Constitution, "The object of the American College of Physicians shall be to establish an organization composed of qualified internists of high standing who shall meet from time to time for purposes of considering and discussing medical and scientific topics, and who through their organization shall attempt to accomplish the further purposes of (a) maintaining and advancing the highest possible standards in medical education, medical practice and clinical research, (b) perpetuating the history and best traditions of medicine and medical ethics, and (c) maintaining both the dignity and efficiency of Internal Medicine in its relationship to public welfare" So reads Article III, Section 1 of the Constitution

By way of fulfilling its destiny, the College holds an annual session of one week each year, publishes an outstanding journal, annually awards certain fellowships and honors and for the last four years has offered its membership a series of postgraduate courses

In the creation of the American Board of Internal Medicine, the College has obligated itself to produce wider opportunities whereby properly qualified aspirants may secure the intensive training and experience which is a prerequisite to certification and fellowship. There is a distinct need for many residencies and fellowships in medicine to furnish adequate facilities for the training of potential internists. Alternative methods of postgraduate training need to be created for men who are not assigned to such appointments

In the 1938 Annual Report of the Commonwealth Fund, the following significant statement is made "Whatever the content, the Division believes that postgraduate study is rewarding, if it brings the student into close personal contact with an outstanding and modern-minded teacher, discipleship plays a large part in medical education, if it helps him to make the best use of books and journals and if it gives him a sound approach to diagnosis"

There is no dearth of courses in the general field of postgraduate education. Various State and County Medical Societies throughout the land are conducting excellent courses for general practitioners. The American College of Surgeons and similar organizations are cognizant of their responsibilities to their membership and to those aspiring for membership. The

¹ Read at the Boston meeting of the American College of Physicians, April 21, 1941

American College of Physicians has a definite obligation in the field of Internal Medicine

In a study entitled "Graduate Medical Education in the United States" published by the Council on Medical Education and Hospitals of the American Medical Association, dealing with the years 1937 to 1940, it was found that there were 110 opportunities for practicing physicians to engage in continuation studies in 43 states, in addition to the District of Columbia, during the 1938-39 period. Forty-four of these courses were sponsored by medical schools, including two graduate schools, and seventeen were offered by medical and clinical societies and academies of medicine. While the subjects of general medicine, obstetrics, pediatrics and surgery were featured, opportunities were also offered for continuing study in seven of the more specialized branches of medicine. Ordinarily membership in a County and State Medical Society is a prerequisite for admission. That these courses are filling a definite need is evidenced by the enthusiasm of those enrolled. From 550 to 600 students, on an average, enrolled for all courses of continuation study in each state, according to the A M A survey.

2 THE AMERICAN COLLEGE AND POSTGRADUATE COURSES

Where does the American College of Physicians fit into this picture? In 1938—four, two week postgraduate courses were conducted under the auspices of the College with an attendance of 117 men, five courses were given with an attendance of 117 men in 1939, five courses were given with an attendance of 130 men in 1940 and eight courses were given with an attendance of 228 students in 1941.

Organizers of these courses and their colleagues have been united in their appreciation of the high quality of training and experience that students enrolled in these courses demonstrated, and, reciprocally, the students displayed unanimous appreciation for the interest shown by their teachers in the conduct of the courses. The development of facilities whereby outstanding teachers have been brought into intimate association with qualified physicians in search of advanced instruction has been spontaneously successful.

There is no need, nor is it desirable, that the American College of Physicians should carry on a crusade or organize a campaign for the purpose of attracting large numbers of students under pressure of high-powered advertising and publicity. Our College should, however, study the interests and organized activities of other national bodies such as the American Medical Association, the American College of Surgeons and similar groups in order to conserve effort and avoid duplication.

It is reasonably safe to assume that the only national organization chiefly interested in the field of Internal Medicine is our own American College. The rapid increase in the number of men who have signified, by a recent questionnaire, that they are looking to the College for the development of opportunities in this field, suggests that our organization has a responsibility it cannot well evade.

3 THE RESULTS OF THE 1940 QUESTIONNAIRE

Soon after President James E Bruce appointed the present Advisory Committee on Postgraduate Courses, a questionnaire, designed to determine the extent of interest of the membership in this field, was sent to every member of the College Of the 918 questionnaires returned, 593 members signified their desire to attend one or more courses under the auspices of the American College of Physicians, 282 men were definite about taking courses, the balance expressed their desire to attend, if possible Interest in the various special fields was as follows

TABLE I

Cardiovascular diseases and electrocardiography	332
Gastroenterology	136
Allergy	67
Endocrine disorders	61
Diseases of the chest	51
Hematology	47
Metabolic diseases	41
Neurology	33
Arthritis and rheumatism	25
Pediatrics	20
Pathology	10

The following outline demonstrates the growth in interest shown by the College membership, since the inception of these courses in 1938

TABLE II

1938

Courses	Time	Conducted By	Attendance		
			Fellows	Associates	Non-Members
General Medicine	2 weeks	Harvard Medical School	31	21	3
General Medicine	2 weeks	N Y Postgraduate	14	11	
Cardiovascular Diseases	2 weeks	University of Pennsylvania	16	8	
Gastrointestinal Diseases	2 weeks	University of Pennsylvania	7	6	3
Total			68	46	
			117*		

1939

General Medicine	2 weeks	Johns Hopkins and Univ of Maryland	17	29	5
Cardiovascular and Respiratory Diseases	2 weeks	Johns Hopkins and Univ of Maryland	11	4	2
Cardio-Renal-Vascular Medicine	2 weeks	Northwestern University	7	14	
Cardiovascular Diseases	1 week	Washington University		11	2
Diseases of the Glands of Internal Secretion	1 week	Washington University	5	9	1
Total			40	67	10
			117†		

TABLE II—Continued

1940

Courses	Time	Conducted By	Attendance		
			Fellows	Associates	Non-Members
General Medicine	2 weeks	University of Michigan and University Hospital	18	15	
Medicine In Industry	1 week	Henry Ford Hospital	3	2	33
Allergy	2 weeks	Roosevelt Hospital	2	6	
Hematology	1 week	Ohio State University	22	15	1
Cardiovascular Disease	1 week	University Hospital, State University of Iowa	16	11	
<i>Total</i>			61	49	34
			144†		

1941

Allergy	2 weeks	Roosevelt Hospital	5	1	2
Gastrointestinal Diseases	2 weeks	Mayo Foundation	18	13	4
General Medicine	3 weeks	Harvard Medical School	21	24	9
Allergy	1 week	Massachusetts General Hosp	6		
Gastro-enterology	1 week	Evans Memorial, Massachusetts Memorial Hospital, Boston University	22	28	
General Medicine	2 weeks	University of Michigan, University Hospital	10	8	6
Clinical Medicine	1 week	Ohio State University	10	11	5
Cardiovascular Disease	2 weeks	University of Pennsylvania, Graduate School of Medicine and University School of Medicine	13	12	
<i>Total</i>			105	97	26
			228§		

In 1938 and 1939 three courses originally offered by the College were withdrawn because of inadequate registrations. In 1941 two courses were withdrawn

* From forty States, Puerto Rico and Canada

† From thirty-four States, Hawaii and Canada

‡ From thirty-three States and Canada

§ From forty-one States, Panama, Puerto Rico, Canada and Mexico

From a brief, albeit enlightening, experience in conducting twenty-two courses during the last four years, certain observations have been made

- (1) It is obviously a distinct pleasure for teachers to have such enthusiastic and well prepared students,
- (2) The smaller the group, the closer the intimacy between instructor and student,
- (3) The students are unified in preferring practical clinical and laboratory experience to didactic lectures,
- (4) The students have but a minor enthusiasm for younger teachers whose chief experience has been in theory,

- (5) The students deeply appreciate suggestions for collateral reading by their instructors,
- (6) The students appreciate the opportunity for social hours at luncheon or in the evening to discuss with their teachers, in an informal way, the various problems and cases of the day,
- (7) The two weeks course is the most popular, although a number of men have requested courses of three and even four weeks' duration,
- (8) While the majority of student physicians desire the courses just preceding the annual clinical session, a number are interested in taking these courses at other times of the year, particularly the men from the South who request that courses be given late in the Spring or in the early Autumn,
- (9) The membership of the College desires to have the courses announced earlier in the year so that appropriate selections and arrangements for participation can be made. There is widespread urge for greater coordination between the courses from year to year and some interest in taking more than one course per year,
- (10) Although some of the students attending courses do not go to the annual session, the majority of those in attendance at the courses do not regard the training as a substitute for attendance at the annual session,
- (11) A number of officials of the College, men who have had experience in medical education, believe that these courses should be organized on a regional or a community basis
- (12) Too great a formalization of courses is not desirable

Because of the limited membership of the College, a course may not draw as large a group of students the second year, as the first year it was scheduled. Experience has shown that for the first year a course may be over-subscribed, the second year those who were not able to enroll previously take the course together with a few more, but the demand is somewhat smaller. Students obviously do not wish to repeat the same course year after year. A reasonable solution to this problem would be to repeat courses every second year, for alternate years, courses along similar lines may be organized at different institutions for students who desire yearly instruction in a particular specialty.

4 THE ADMITTANCE OF NON-MEMBERS TO COURSES

Frequently requests have been received from non-members for admission to courses conducted under the auspices of the American College. The Board of Regents has made a rule that only Fellows and Associates of the College be admitted to these courses. However, if there is room up to capacity after all members desiring to attend have enrolled, under certain conditions non-members have been admitted. In view of the fact that these courses are excellent supplementary preparation for serious minded younger

doctors who are anticipating the examinations to be given by the American Board of Internal Medicine, it may be possible to develop means whereby non-members with proper qualifications and necessary direction, may, upon recommendation by an Officer, Regent or Governor of the College, be admitted to courses

5 REGENCIES

Several members of the American College of Physicians whose experience in medical education qualifies them as experts, have suggested the advisability of dividing the United States and Canada into geographical areas known as Regencies. A Regent of the College would be assigned the responsibility of organizing the Governors in his particular Regency into a Regional Committee. In addition to other duties, which are purely of a regional or local nature, the direction of interest of these committees would be to study the needs of the College membership in their section and encourage participation in the problem of postgraduate training. With the continued growth of the American College and the increasing complexity of its executive direction, the Regents and Governors may anticipate heavier responsibilities in the formulation of policies and the conduct of its activities. Even now postgraduate training under the auspices of our organization might be more satisfactorily studied on a sectional or regional basis.

6 CLINICAL VERSUS RESEARCH TRAINING

Officials of the American College of Physicians are uniform in their desire to foster clinical training and develop first class clinicians rather than to concentrate on the training of research-minded laboratory workers. One official stated that it would be easier and more practical to assist in the education of 20 competent internists per year than develop one investigator. Another official believes that postgraduate training by the American College should include the granting of clinical Fellowships whereby younger men would have an opportunity to pursue advanced work along a well coordinated program.

7 COLLATERAL READING

In certain of the courses, the Directors have given student physicians definite suggestions concerning collateral reading to be carried out in association with their studies. These suggestions have been enthusiastically received. One recalls that collateral reading is an important part in the training of candidates for Fellowship in the Royal Colleges of England, Scotland and Canada.

In view of the endless variety in the quality and quantity of reading material in the broad field of Internal Medicine today, the membership of the College at large would, no doubt, find it generously beneficial if throughout the entire year a course of selected collateral reading might be offered through the Annals of Internal Medicine. This, in effect, would constitute

a reasonably satisfactory extension course for many of the members who cannot avail themselves of opportunities for participation in postgraduate training. A number of university departments throughout the nation are today conducting similar courses in collateral reading to the eminent satisfaction of a large following.

8 FINAL IMPRESSIONS

Probably the major objective of the American College of Physicians lies in the field of medical education. This, as explained by President Bruce, should consist of postgraduate opportunities whereby its members may be kept constantly abreast of medical progress, and, also, longer and more intensively arranged opportunities by which suitable aspirants may prepare themselves for specialism in Internal Medicine and its allied fields.

Valuable as postgraduate courses are in the maintenance of standards already achieved, they are but supplemental to effective graduate courses of study, whether the latter be formal courses now existing, or an orderly arrangement for study with competent men in well organized hospitals with university or medical school affiliations.

The American College of Physicians is the only organization whose principal interest is the continuous training of the internist.

The American College of Physicians is primarily interested in training clinicians rather than research students or teachers.

The Committee on Postgraduate Courses has recommended that for the next year the following courses be offered under the auspices of the College:

- | | |
|------------------------------|--|
| (a) General Medicine | —2 courses—2 weeks in duration |
| (b) Allergy | —2 courses—2 weeks in duration |
| (c) Cardiovascular Disorders | —2 courses—2 weeks in duration |
| (d) Gastroenterology | —2 courses—1-1 week, 1-2 weeks in duration |
| (e) Arthritis and Rheumatism | —1 course —1 week in duration |
| (f) Tuberculosis | —1 course —1 week in duration |

In view of the growth of the College and the increasing complexity of the problem of postgraduate studies, it is recommended that a regional division of the College be considered.

The possible curtailment of courses depends on the national situation. Courses in collateral reading should be developed and published in the *Annals*.

The American College should consider ways and means, as suggested in a resolution by the Board of Regents at their December 1940 meeting, for offering courses in advanced medicine for the personnel of army hospitals associated with the mobilization of the nation's resources.

In establishing the habit of scholarship, under capable guidance, the student physician in the final analysis must be his own teacher.

CASE REPORTS

RUPTURE OF AORTA INTO THE PULMONARY ARTERY WITH LONG SURVIVAL *

By PAUL D WHITE, M D , F A C P , FRANCIS L CHAMBERLAIN, M D , and
SAUL R KELSON, M D , *Boston, Massachusetts*

CASE REPORT

JOSEPH Meranda, negro, 74 years old at death in 1938, a Cape Cod cranberry picker, entered the Massachusetts General Hospital in November 1933, in his seventieth year, because of ulcers of the right leg following varicose veins and an infected scratch of a year before. He had had no dyspnea, chest pain, or palpitation, but examination revealed moderate enlargement of the heart, aortic systolic and diastolic murmurs, a blood pressure of 195 mm mercury systolic and 55 mm diastolic, a positive Hinton reaction, and by roentgen-ray slight aneurysmal dilatation of the ascending aorta (figure 1 A). In three weeks he was discharged with the ulcers almost wholly healed after treatment by rest, potassium iodide and mercury by mouth, and soothing ointments to the leg. He continued the potassium iodide and mercury for a few months.

Early in January 1937, a little over three years later, he was taken ill with what he thought was a cold, accompanied by palpitation and dyspnea to the point of orthopnea. A short rest in bed helped temporarily, but a few months later, in April, he grew much worse, with substernal pain and restlessness quickly followed by edema of the legs. In May 1937 he reentered the Massachusetts General Hospital very ill. His heart was found to be much larger, the murmurs were described as before, and the roentgen-ray (figure 1 B) showed marked prominence of the pulmonary artery and lung hilus shadows not present in the earlier picture. He improved rapidly under rest, digitalization, and salyrgan diuresis, and was discharged in a few days. He remained improved for six months.

In January 1938, he rapidly grew worse again and reentered the hospital in February in severe congestive failure. Physical examination is said to have shown the same auscultatory findings as before, but this time an "aortic" systolic thrill was noted in addition. The blood pressure varied from 130 to 180 mm mercury systolic and measured about 60 mm mercury diastolic. The electrocardiogram was not remarkable. On February 2, Dr Sprague noted that the murmur and thrill in the pulmonary area were really continuous and not just systolic and diastolic as previously described. On February 8, we hazarded the diagnosis of "rupture of an aortic aneurysm into the pulmonary artery." This, we went on to say, "and only this, will explain the continuous character of the murmur and thrill in the pulmonary valve area and the appearance by roentgen-ray of a marked bulge in the pulmonary conus not in the least apparent in 1933. Careful fluoroscopy when he improves enough to allow it would help in establishing or rejecting this diagnosis. The murmur sounds like that of a patent ductus arteriosus which, condition, however, was not evident by roentgen-ray in 1933." Fluoroscopy on March 1 confirmed this impression.

* Received for publication May 1, 1941

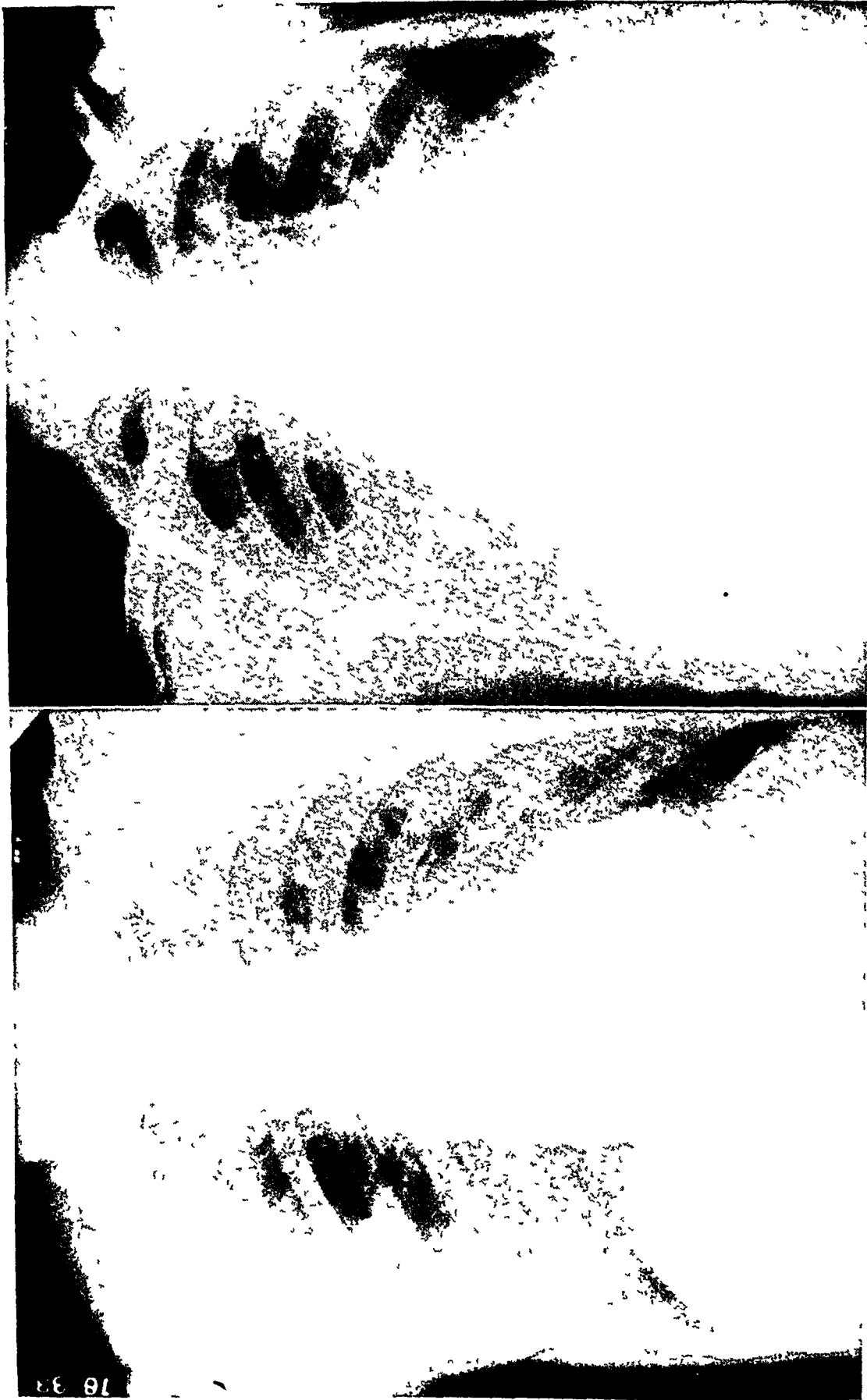


FIG 1 A Roentgen-ray film showing slight cardiac enlargement and slight widening of the great vessels of J M, November 1933

FIG 1 B Roentgen-ray film showing marked increase in heart size particularly with bulging in the region of the pulmonary artery of J M, May 1937



FIG 2 Anterior view of right ventricle and right auricle of J M, opened to show normal valves, hypertrophied and dilated ventricle, and a small hole just above the pulmonary valve connecting the pulmonary artery with the aorta. Probe is shown inserted into this opening.

He continued completely crippled with heart failure after he went home and died on October 7, 1938, 21 months after the onset of his heart symptoms and eight months after the clinical diagnosis was made of rupture of an aortic aneurysm into the pulmonary artery.

AUTOPSY

The body was that of a well nourished, 74 year old male negro slightly over six feet tall and weighing approximately 200 pounds. The heart weighed 885 grams, and was greatly enlarged in all diameters, with particular prominence in the region

of the pulmonary conus. Its cavities had approximately three times normal volume, and all valve rings were dilated. The left ventricular wall measured up to 19 mm in thickness, the right up to 7 mm. The mitral and tricuspid valve cusps were slightly edematous but otherwise negative. The pulmonary valve appeared normal. The aortic valve was slightly thickened along its free edge. The aortic sinuses were greatly dilated, with a few small nodular calcific deposits at the base of the right and posterior cusps. The myocardium showed no gross scarring on section.



FIG 3 View of left ventricle and aorta of I M opened to show much dilated left ventricle, normal mitral valve, essentially normal aortic valve and dilated aorta with an aneurysmal pouch at the left in which is seen an opening leading into the pulmonary artery

Coronary Arteries The orifice of the right coronary artery was completely occluded by syphilitic and atherosclerotic scarring, and the vessel itself was small and collapsed. The left coronary artery ostium was highly placed, 1.5 cm above the aortic ring; this artery was patent throughout and showed only very slight atherosclerosis.

Pulmonary Artery The pulmonary artery was markedly dilated, measuring 8.5 cm in circumference at a level 3 cm above the pulmonary valve ring. Five mm above the insertion of the valve cusps and slightly posterior and to the right of the right anterior pulmonary valve commissure was a roughly oval opening 5 mm by 6 mm with smooth, slightly raised margins (figure 2). The artery was otherwise free



Fig 4 Closer view of aneurysmal pouch of aorta with sinus leading into the pulmonary artery

Aorta There was marked diffuse aneurysmal dilatation of the ascending aorta and arch, and to a lesser extent, of the descending portion. The aorta and arch showed changes typical of syphilitic aortitis: there were numerous linear, puckering, spoke-like crenations, and smooth pearly elevated patches, with many soft yellow atheromatous deposits, ulcerated in places. Above the right posterior commissure was a secondary saccular aneurysmal pocket 2.3 cm across by 2.8 cm high by 2.1 cm deep, with thickened smooth edges. A probe within the right coronary artery passed behind and above this sac to an occluded orifice immediately to the right. Above the commissure between the right and left anterior cusps was a less sharply defined secondary aneurysmal pouch, measuring 3.5 cm across, by 4.0 cm long, by 2.0 cm deep, with a small out-pocketing from its upper right margin. In its anterior lower margin, 1.5 cm above the aortic valve ring, was a smooth-edged oval opening, surrounded by puckered yellowish plaques. This opened into the pulmonary artery (figures 3 and 4), and was the same opening previously described there. Above and slightly to the left of the posterior aortic cusp, with its lower margin 1.7 cm above the free edge of the cusp, was a smooth-lipped opening into the aortic wall, 9 by 7 mm. This ended in a blind pocket in the septum between the aorta and right auricle, with a depth of 3 mm, partly filled with projecting irregular clot. The descending aorta measured 7.5 cm in circumference, and showed numerous atherosclerotic plaques but very few puckerings suggesting syphilis. Atheromatous changes were most plentiful in the abdominal aorta, particularly at its bifurcation, where ulceration was extensive.

Venae Cavae The venae cavae appeared normal.

Microscopic Examination Myocardium The heart muscle showed one small area of fibrosis. The small branches of the coronary arteries appeared normal.

Aorta The aortic wall showed perivascular lymphocytic infiltration characteristic of syphilis. There was fragmentation of the elastic fibers with medial degeneration and hyalinization. There were areas of intimal thickening and hyalinization, and extensive areas of cholesterol deposit deep in the media, with necrosis of the surrounding tissue and a few small foci of calcification in the media.

DISCUSSION

In the last 25 years there have been a dozen case reports of this rare condition, the last one in 1938. Before 1913 there had been about 50 cases on record. Only two previously, so far as we know, have been definitely diagnosed antemortem, a porter aged 35 by Wade of England in 1861, and a negro aged 29 years reported by Scott of Cleveland in 1924*. However, the chief diagnostic clue, namely, the development of a continuous murmur in the pulmonary valve area, was clearly pointed out by James Hope in 1839 in the third edition of his work on diseases of the heart and great vessels.

Our case was relatively easy to diagnose because of the long survival and the opportunity we had to examine the patient before and after the rupture (including the comparison of the roentgen-ray films). The long survival was doubtless due in part at least to the small opening from the aorta into the pulmonary artery.

Of the 13 cases noted in the last 25 years, six were negroes, only five of the 13 lived more than two months after the beginning of symptoms. The duration of life in the 13 cases was apparently three for a few hours, one for 24 hours, one for three weeks, another for three weeks, and the others for five weeks,

* Since this report was written another case has been correctly diagnosed antemortem by Dr William Porter of Richmond, Va (personal communication).

two months four months, four months, nine and a half months, 11 months, and 4 years respectively, the last case was not correctly diagnosed antemortem. Thus our case was very unusual with his survival of 21 months after the onset of symptoms and eight months after the correct clinical diagnosis. The case that survived a long time (4 years) had a smaller opening, 7 mm in diameter.

SUMMARY

A case is reported of a negro who died of heart failure at 74 years of age, 21 months after the onset of cardiac symptoms and eight months after the correct clinical diagnosis was made of rupture of a syphilitic aneurysm of the ascending aorta into the pulmonary artery. This case is of note first and especially because of the unusual longevity both in age of patient and in survival after the rupture, and second, because only two cases previously had been correctly diagnosed antemortem. The clinical diagnosis of a small rupture of the aorta into the pulmonary artery was apparent from the combination of the development of a continuous murmur in the pulmonary valve area, the bulging pulmonary artery by roentgen-ray, and the rapid appearance of congestive heart failure without early fatality in a negro with known syphilitic aortitis.

REFERENCES

ARRANGED CHRONOLOGICALLY

- 1 WELLS, WILLIAM C. Trans of a Soc for the Promotion of Med and Chir Knowl, 1812, iii, 85
- 2 REID, J. Case II. Aneurysm of the aorta bursting into the pulmonary artery, Edinburgh Med and Surg Jr, 1840, liii, 99
- 3 REID, J. Case III. Aneurysm of the aorta communicating with the pulmonary artery, Edinburgh Med and Surg Jr, 1840, liii, 101
- 4 REID, J. Case IV. Aneurysm of the arch of the aorta bursting into the pulmonary artery, Edinburgh Med and Surg Jr, 1840, liv, 114
- 5 HENDERSON, WILLIAM. On the sounds afforded by substernal aneurysms, Edinburgh Med and Surg Jr, 1840, xlv, 322
- 6 THURMAN, J. On aneurysms and especially spontaneous varicose aneurysms of the ascending aorta and sinuses of Valsalva with cases, Med Chir Trans, London, 1840, xxiii, 323
- 7 SMITH, MR. Varicose aneurysm communication with the aorta and pulmonary artery, Dublin Med Jr, 1840-41, xviii, 164
- 8 HOPE, J. A treatise on the diseases of the heart and great vessels, Third Edition, 1839, J Churchill, London
- 9 TURNBULL, JAMES. Cases of disease of the heart and aorta, Lancet, 1845, ii, 91
- 10 ROKITANSKY, C. F. Im 4 Bd Denk d math Klass der K Akademie der Wissenschaften, Wien, 1852
- 11 OGLE, J. W. Specimen of aneurysm of the ascending aorta communicating with the pulmonary artery, Trans Path Soc London, 1852, iv, 114
- 11 a HERAPATH, W. B. Case of rupture of an aneurysm of the transverse portion of the arch of the aorta into the trunk of the pulmonary artery, Assoc Med Jr, 1853, p 683
- 12 BENNETT, J. H. Clin Lect on Princ and Pract Med, Edit S S and W Wood, New York, 1859, iii, 595
- 13 PIERRESON, M. A. Aneurysme de l'aorte communicant avec l'artere pulmonaire, Bull Soc Anat de Paris, 1860, xxxv, 198

- 14 WADE, W F On a case of aortic aneurysm in which a communication with the pulmonary artery was recognized during life by means of physical diagnosis, *Med Chir Trans*, London, 1861, xlv, 211
- 15 ROBERTS, WILLIAM Case of aneurysm of ascending aorta communicating with pulmonary artery, *Brit Med Jr*, 1868, 1, 421
- 16 PEACOCK, T B Aneurysm of the ascending aorta pressing upon the base of the right ventricle and opening into the origin of the pulmonary artery, *Trans Path Soc London*, 1868, xix, 111
- 17 MURCHISON, CHARLES Aneurysm of the ascending aorta opening into the pulmonary artery, *Trans Path Soc London*, 1868, xix, 190
- 18 CAYLEY, W Aneurysm of the ascending aorta communicating with the pulmonary artery, *Trans Path Soc*, London, 1870, xxi, 122
- 19 REEVES, C E Observations on aneurysm of the aorta, *Heart Diseases of Australia*, Published by Author, J Brooks, Australia, 1873, p 125
- 20 FINNY, J M Aortic aneurysm communicating with the pulmonary artery, *Dublin Jr Med Sci*, 1880, lxx, 170
- 21 WEST, SAMUEL Aneurysm of the aorta rupturing into the pulmonary artery, *Trans Path Soc*, 1882-83, xxxiv, 64
- 22 TAYLOR, F Cases of aortic aneurysm opening into the pulmonary artery, *Guy's Hosp Rep*, 1883-1884, xlii, 391
- 23 HANDFORD, H Aneurysm of the aorta communicating with the pulmonary artery, *Edinburgh Med Jr*, 1888, xxxiii, 695
- 24 ANDERSON, JOHN A A case of aneurysm of the aorta perforating the pulmonary artery, *Glasgow Med Jr*, 1888, xxx, 283
- 25 KRAUSSOLDT, THEODOR Ueber einen Fall von Aneurysma der Aorta mit Perforation in die Pulmonalarterie, 1893, *F Junge, Erlangen*
- 26 LAMPLOUGH, C Cases of aneurysm of the aorta communicating with the pulmonary artery, *Brit Med Jr*, 1897, ii, 392
- 27 GAIRDNER, W T Case of a small aneurysm of the first part of the arch of the aorta opening into the pulmonary artery and conus arteriosus of right ventricle with remarks on the general subject, *Glasgow Hosp Rep*, 1899, ii, 1
- 28 CLARKE, J M A case of varicose aneurysm of the aorta communicating with the pulmonary artery, *Brit Med Jr*, 1900, ii, 1701
- 29 HODLMOSER, C Beitrag zur Symptomatologie und Diagnose der in die Pulmonalis perforirenden Aneurysmen der Aorta ascendens, *Ztschr f klin Med*, 1901, xlii, 251
- 30 SMITH, F J A case of aneurysm of the aorta rupturing into the pulmonary artery associated with fibrosis of one lung, *Lancet*, 1904, 1, 1119
- 31 McNABB, D Case of aneurysm opening from the first part of the thoracic aorta into the pulmonary artery, *Brit Med Jr*, 1905, 1, 883
- 32 KAPPIS, M Die Perforation eines Aortenaneurysmas in die Pulmonal-Arterie, *Deutsch Arch f klin Med*, 1907, xc, 506
- 33 LENOBLE and CHAPEL Periviscérites disséminées à forme de symphyse péricardoperi-hepatique aneurisme sacciforme et communication avec l'artère pulmonaire, sans maladie bleue, *Bull et mem Soc méd d hôp de Paris*, 1909, xxviii, 494
- 34 HOLLIS, A U Aneurysm of aorta perforating into pulmonary artery, *St Luke's Hosp Med and Surg Rep*, New York, 1908-9, 1, 168
- 35 STEVENSON, H N Aortic aneurysm rupturing into the pulmonary artery with a report of three cases, *Bull Johns Hopkins Hosp*, 1913, xiv, 217
- 36 WOOLEY, P G A series of ruptured aortic aneurysms, *Am Jr Syph*, 1917, 1, 426
- 37 JANKOVICH, L In die Arteria pulmonale perforierende Aorten-aneurysmen, *Wien klin Wchnschr*, 1918, xxxi, 73
- 38 STERNBERG, H Ueber zwei Fälle von Durchbruch der Aorta in die Arteria pulmonalis, *Wien klin Wchnschr*, 1919, xxxii, 1024

- 39 SCOTT, R W Aortic aneurysm rupturing into the pulmonary artery, Report of two cases, Jr Am Med Assoc, 1924, lxxxi, 1417
- 40 KORB, C, and ALMAN, D Aortic aneurysm rupturing into the pulmonary artery, report of a case, New England Jr Med, 1928, cxviii, 280
- 41 CLERC, A, BASSOURET, M, and FROUZE, R Communication between aorta and pulmonary artery following ruptured aneurysm, survival of patient for more than 4 years, Bull et mem Soc med d hôp de Paris, 1931, lv, 1288
- 42 CORREIA Rev d Assoc paulista de med, 1933, ii, 321
- 43 PORTER, D L Rupture of aortic aneurysm into pulmonary artery, Trans Chicago Path Soc, 1935, xiv, 240
- 44 DELP, M H, and MAXWELL, R Rupture of an aortic aneurysm into the pulmonary artery, Jr Am Med Assoc, 1938, cx, 1647

A FATAL CASE OF BESNIER-BOECK-SCHAUMANN'S DISEASE WITH AUTOPSY FINDINGS *

By FREDERICK TICE, M D, F A C P, and HENRY C SWEANY, M D, F A C P,
Chicago, Illinois

NEW facts are forever widening the horizon of knowledge. What is thought to be pathognomonic of a disease today may be changed tomorrow to a presumptive sign or, with new data, may present an entirely new syndrome or disease complex.

These statements are strikingly applicable to a hodge-podge of syndromes which have been unfolding themselves during the last half century and have been reported by Besnier,¹ Boeck,² Schaumann³ and others. A disparity of views has resulted because only a small part of the complete knowledge was known at any time. It is comparable to Aesop's fable concerning the color of the chameleon. Erythema induratum of Bazin (1861), the chillblain lupus of Hutchinson (1888), the lupus pernio of Besnier (1889), miliary lupoids and sarcoids of Boeck (1899), subcutaneous sarcoids of Darier-Roussy (1904), granuloma annulare of Little (1908), angio-lupoid of Brocq and Pautrier (1913), and several other types of skin lesions were at first considered as variations of lupus. Although there is still a wide divergence of opinion as to the nature of some of the above mentioned skin conditions, they have been gradually separated from the definitely tuberculous lesions such as the tuberculides, the miliary lupoids of Boeck, and others. Schaumann further set apart the chillblain lupus of Hutchinson, the subcutaneous sarcoids of Darier and Darier-Roussy, granuloma annulare and skin conditions attributable to syphilis, and retained only the lupus pernio of Besnier and the large nodular sarcoids of Boeck as a part of a new disease entity which he has called "benign lymphogranulomatosis" in contrast to the malignant form of Hodgkin's disease. Pautrier⁴ at first included most of the above mentioned forms in the true sarcoids but, as shown by Tüllgren,⁵ he has gradually come over toward Schaumann's point of view. In 1934 he still retained "the subcutaneous sarcoids" in addition to lupus pernio and Boeck's large nodular sarcoid.

* Received for publication March 30, 1940

From the Clinical and Laboratory Departments of the City of Chicago Municipal Tuberculosis Sanitarium

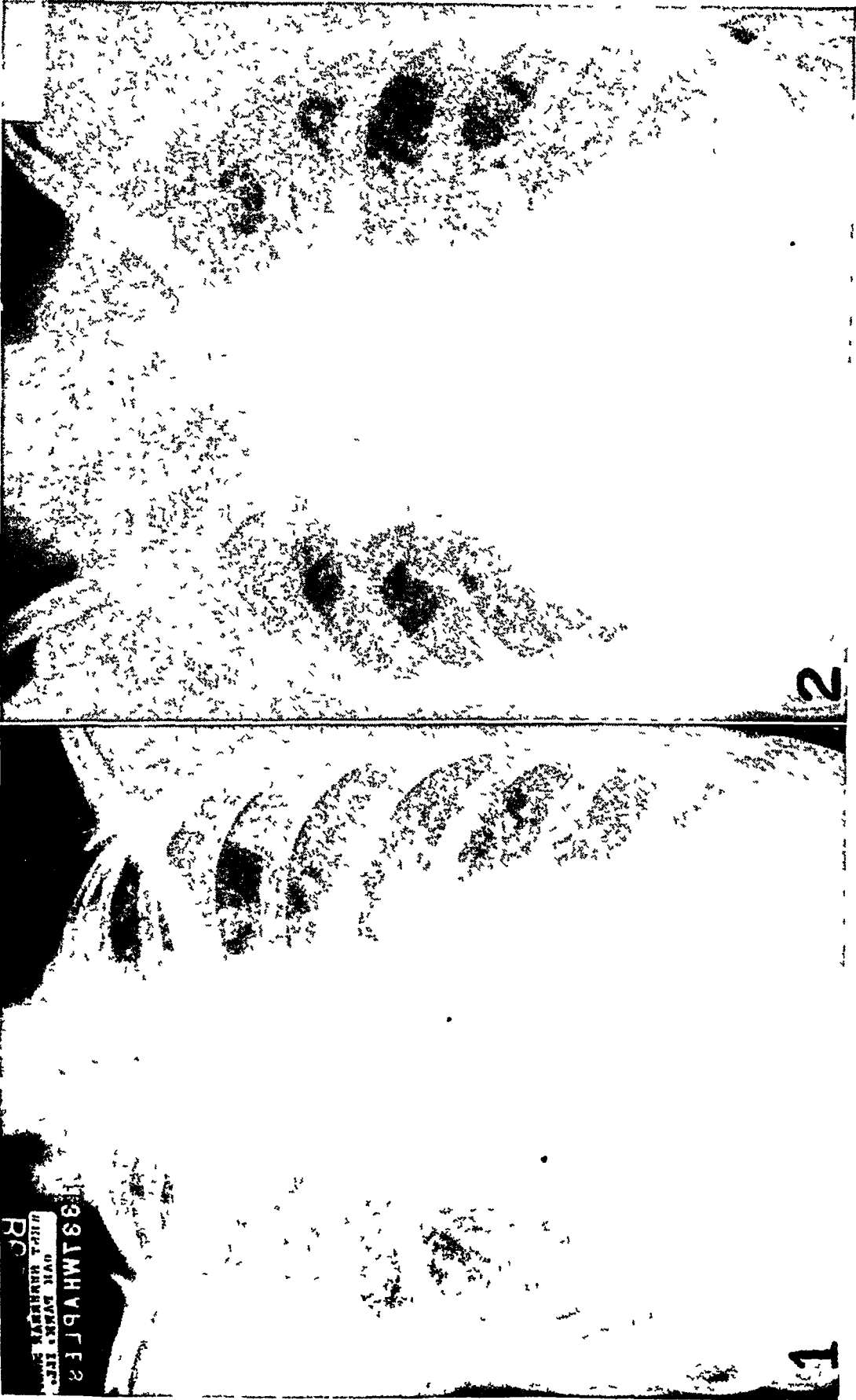


FIG 1 (1) Roentgenogram taken April 13, 1937, revealing an appearance of "fibroid" tuberculosis (2) Another roentgenogram, taken January 9, 1939. There is a great deal of clearing of parenchymal lesions but a pronounced increase in the density out from the midline on the right side

Without doubt the greatest advance with regard to the nature of "sarcoids" was the pronouncements of Schaumann that they were part of a systemic process. At first Boeck suggested that they might be systemic, but later retracted the suggestion. The bone lesions were the first observed apart from the skin lesions, but were not at first understood as part of a systemic disease. Although Kienbock (1902),⁶ Kreibich (1904),⁷ Bloch (1907),⁸ Rieder (1910),⁹ and Jungling (1921)¹⁰ reported bone lesions alone or associated with lupus pernio, Schaumann (1914)¹¹ was the first to consider them as part of a general process wherein there is usually a lymphadenopathy, as well as lung and tonsillar lesions. Less commonly there may be skin lesions, bone and marrow changes, enlarged spleen and liver, lesions of the mucous surfaces, the uveal tract, the parotid, and many other organs of the body. There is nearly always a mononucleosis associated with the other lesions. It seems to be logical that the adenopathy should appear as part of the first generalization of the disease, with lung, skin, bone, and other lesions appearing at various intervals later.

The greatest controversy has taken place regarding the nature and cause of "sarcoids." Many French clinicians (Darier,¹² Pautrier,¹³ Gougerot,¹⁴ et al.) have considered that the disease is a reaction of the host and not caused by any single agent. Among the probable causes they mention tuberculosis, leprosy, syphilis, foreign bodies (paraffin, vaseline) and leishmaniasis. Some feel that it is caused by a filtrable form of the tubercle bacillus while others consider, with justification, that the cause is still unknown.

Kissmeyer¹⁵ believes that sarcoid is due to an unknown virus with effects ranging between those of leprosy and tuberculosis. Kuznitzky and Bittorf¹⁶ think it is a disease sui generis. Schaumann at first felt that it was such a condition, but later considered it due to tuberculosis possibly of the bovine type. The trend now seems to be in favor of a tuberculous origin, though there are many other widely different theories. It does seem, that in view of the variations of the tubercle parasite, which have been demonstrated by many bacteriologists, there may well be variable pathologic and clinical effects depending upon these variations.

Many cases have now been followed for years in which there has been a gradual change noted from the "sarcoid state" or "benign lymphogranulomatosis" of Schaumann to some form of tuberculosis with a demonstration of the parasites, a changing of a negative to a positive tuberculin reaction, and along with this and perhaps as a result of it, the occurrence of caseation. Kyrle¹⁷ among others has followed the aging of the lesions from the early focal point of lymphocytes through the appearance of monocytes to the development of giant cells. The latter forms mature and disintegrate, after which fibrosis develops in the old focus. Kyrle also reports the presence of tubercle bacilli during the early stages of development but a disappearance of the bacilli as the nodules reach the stage of giant cells and fibrosis. Our own work at the Municipal Tuberculosis Sanitarium has partly borne this out as well as permitted us to observe other additional phenomena of even greater interest.

Most observers are agreed with respect to the histology of sarcoids. In fact, there is little other choice because the findings are quite constant. The lesions consist of milary nodules that form first as monocytic accumulations and then develop into Langhans' giant cells with a few lymphocytes. The giant cells become older, get large and disintegrate, leaving a fibrous nodule without caseation.

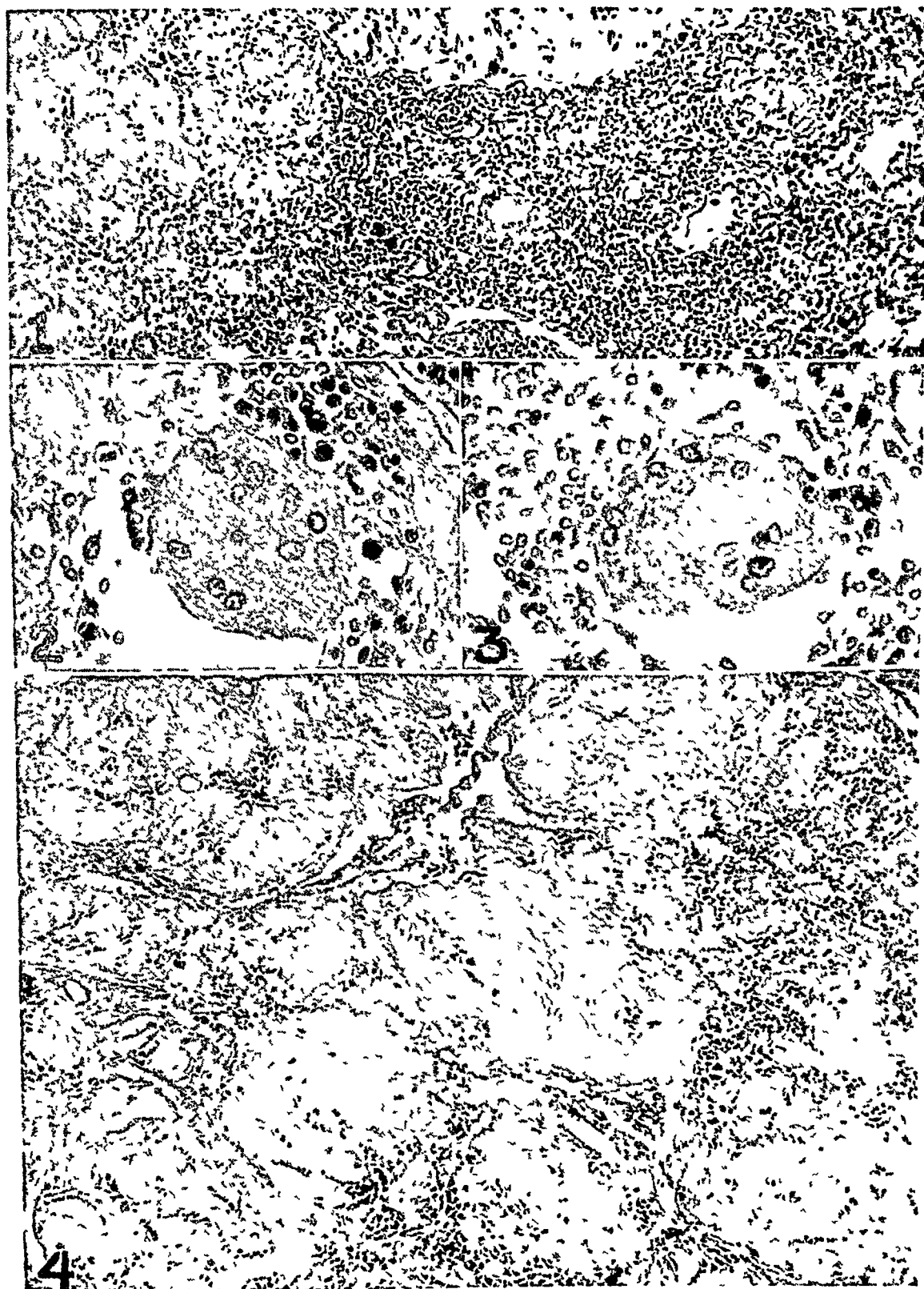


FIG 2 (1) A photomicrograph of section of lymph node showing small foci of inflammation, hyaline connective tissue fibers, and Langhans' giant cell $\times 130$ (2 and 3) Two "old" giant cells undergoing disintegration $\times 400$ (4) Fibrous residue in a lymph node in which the lesions have run their course $\times 120$

Because of these characteristics, Mylius and Schurmann¹⁸ have used the cumbersome term of "widespread sclerosing tuberculous giant cell hyperplasia." Much more appropriate is Pinnei's¹⁹ term "non-caseating tuberculosis."

The presence of caseation is ordinarily understood to rule out the diagnosis of sarcoid. However, as certain cases become tuberculous, they develop caseation, when they do, they automatically cease to be "non-caseating." Likewise, in the opinion of many, they would cease to be "sarcoid." It is obvious that the terminology cannot be definitely settled until the etiology and complete course of the disease are known.

The important feature in this report concerns the lung lesions, especially those of a late evolutionary stage. Although Schaumann first mentioned lung lesions in 1914, Kuznitzky and Bittorf, in 1915,¹⁰ deserve most credit for an accurate description of the process.

The early lung lesions appear on roentgenograms usually as soft nodules simulating disseminated tubercles or small soft infiltrates with an associated hilum lymph node enlargement. These lesions are perhaps the same as the vast number of benign miliary tubercles of the lung, or healed miliary tuberculosis described as *miliare froide* by Sayé and Burnand, as *miliaris discreta* by Neumann, and in still other terms by others. As the lesions become chronic there is a disappearance of their "soft" nature and the appearance of a stringy and net-like fibrosis over the entire lung fields, especially out from the hilum. A late emphysema usually appears. The microscopic appearance corresponds to these findings. There is a transition from the cellular nodule to the fibrotic one.

The report we are about to make concerns strictly the roentgen-ray and pathological findings of the lungs, although there are other useful data concerning the gross findings in the other organs, and the clinical course. Due to the fact that much of the clinical data was not available, no claim at completeness is made for anything except the roentgen-ray and the pathological findings in the lungs and thoracic lymph nodes.

There is a secondary interest in the heart lesions also because of the effect which the lung fibrosis exerted on cardiac function. Nothing was observed in the way of specific heart lesions, as reported by Salveson²⁰.

Owing to the fact that few autopsies have been reported on this condition, no efforts should be spared to report every case about which any complete data are available. Only 18 autopsies had been reported by 1938, according to Pinnei.¹⁹ Spencer and Warren²¹ have added one since. Although there is much of interest in the gross findings in the organs, microscopic notes are available only for the lungs and lymph nodes. While no skin lesions were ever reported and no observations, clinical or pathological, were ever made which indicated the presence of other lesions than those in the lungs and hilum lymph nodes, it must be admitted that a more complete history and a more complete microscopic study might have revealed facts that were not evident.

CASE REPORTS

The patient, a 45 year old woman, was seen by one of us (T) in consultation with Dr. John W. Tope on April 16, 1937. She had been ill four months with cough and dyspnea, but no fever. Six sputum examinations were negative for tubercle bacilli. Two recent roentgen-ray films revealed mediastinal shadows, more on the right than on the left. There were irregular infiltrations in the lung fields. There



FIG 3 (1) A low power photomicrograph of lung tissue. Note the marked perivascular fibrosis. $\times 8$. (2) An enlargement of the part outlined in part 1. The focal nature of the fibrosis is more evident. Early lesions may be seen in the lymphoid tissue in the right upper corner. $\times 31$.

were no cervical or axillary glands and no enlargement of the spleen. The earlier diagnosis by Drs. Tope and French had been pulmonary tuberculosis. Because of the negative sputums and rather characteristic hilum shadows a diagnosis of Hodgkin's disease was made, for which the patient subsequently received roentgen-ray therapy which temporarily relieved her dyspnea. At a later date her dyspnea apparently recurred and a reported diagnosis of Ayerza's disease was made*. She was sent to Valmora Sanatorium where death occurred suddenly in bed on March 6, 1939.

The first roentgenogram was taken April 13, 1937. The bony framework appeared normal except that there was a droop to the right shoulder and a slight narrowing of the intercostal spaces on the right side. There was a slight scoliosis. The heart was partly concealed in a hazy jagged mass around the hilum. The right hilum was much more involved than the left. There was a partly consolidated mass extending from the apex to the base paralleling the spine and extending laterally several centimeters. The upper and middle lobes were extensively involved in a large nodular and infiltrative involvement that appeared almost confluent except in the apex. The nodules were on the average about 5 mm. in diameter, but were irregular, had hazy and irregular borders, and seemed to blend out into the perivascular shadows. The lower lobe was also involved in a similar manner but only to about one-half the density. No definite annular shadows were visible. In the left lung there were dense streamers of densities extending from the hilum out toward the axilla and to a lesser extent toward the apex and base, flanked by the same vague irregular nodules described on the other side.

A roentgenogram taken September 20, 1937 revealed a slight clearing of the nodular densities with a slight exaggeration of the perivascular shadows.

A roentgenogram taken September 8, 1938 revealed an extension of the atelectasis at the right base half way across the visible lung field, and then up toward the hilum where a large mass was observed protruding outward. There was a fading off of the density toward the apex. Outside of a few nebulous clouds in the right upper lobe and an increase in the left hilum density, there was little change.

The last roentgenogram, taken January 9, 1938, showed an exaggeration of the condition described before. The hilum mass at this time extended half way out and the basal mass three-fourths of the way out to the lateral wall. The scoliosis was exaggerated, the trachea was pulled over to the right. The upper lobe was more dense, but a few irregular clear spaces appeared in the midfield which were perhaps emphysematous bullae rather than true cavities. The left side was not greatly changed.

An autopsy was performed by Dr. R. Yale Lyman, and the protocol was furnished through the courtesy of Dr. C. H. Gellenthien of Valmora, New Mexico.

Autopsy. G. W. was a white female housewife who was 48 years old at the time of death. The diagnoses on admission to the sanatorium were pulmonary tuberculosis, Hodgkin's disease, Ayerza's disease and mediastinal tumor.

The external examination revealed a slender emaciated white female about 50 years of age. There was a slight yellowish pigmentation of the skin. The hair was brown and the pupils dilated.

There was moderate kyphosis of the thoracic spine. The abdomen was flat. The remainder of the external examination was negative.

Examination of the thoracic cavity revealed 200 c.c. of straw-colored fluid in the left pleural cavity and 500 c.c. of reddish fluid in the right. There were adhesions between the anterior surface of the pericardium and sternum.

The right lung was contracted and drawn to the right side of the mediastinum. The left lung overlapped the mediastinum to the right border of the sternum. There was a fatty globular remnant of the thymus located in the superior ventral portion of the mediastinum.

* Since the preliminary report it has been learned that Dr. E. E. Irons was responsible for this accurate clinical observation.

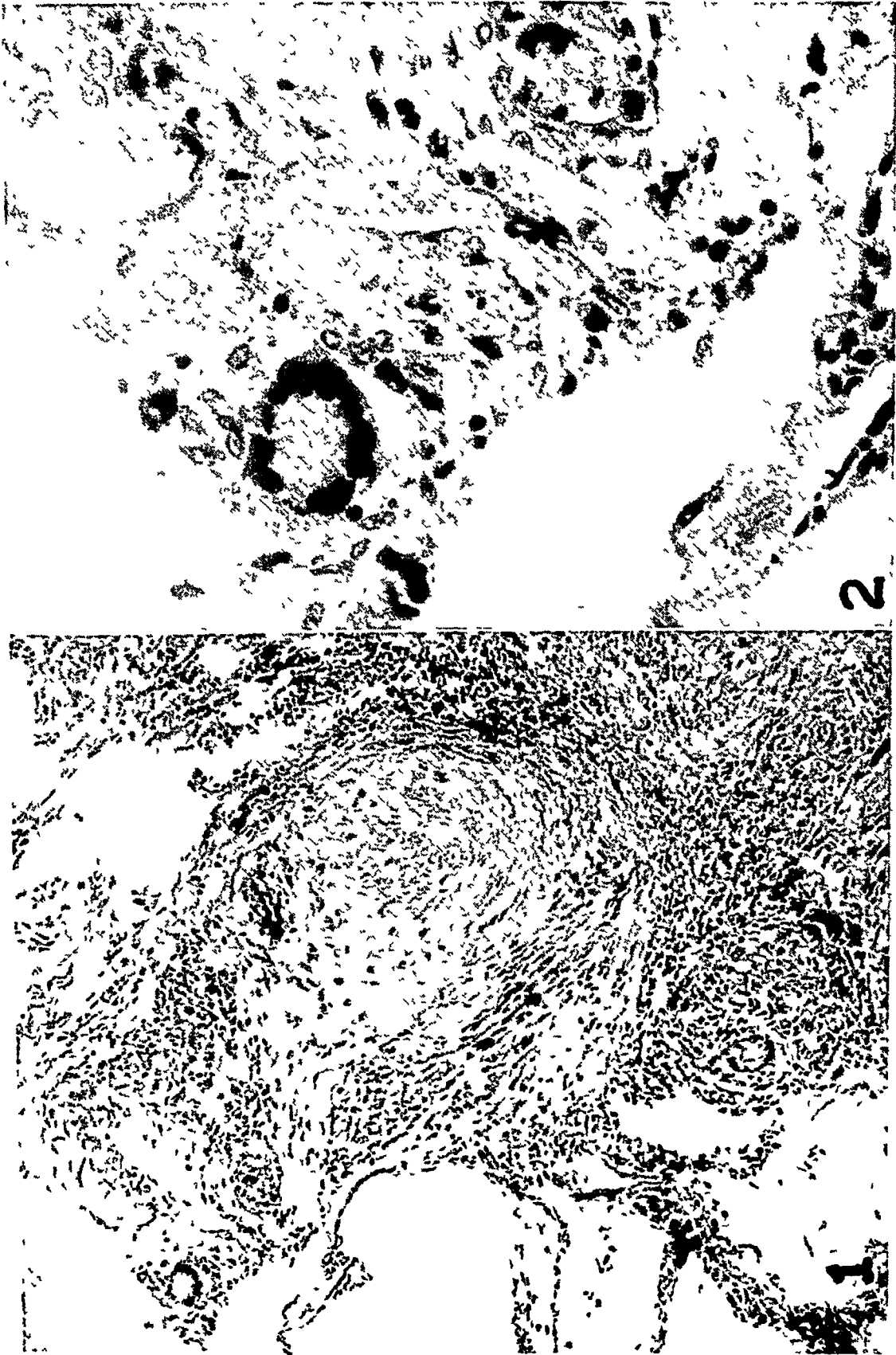


FIG 4 (1) A higher power of the area outlined in figure 3 (2) Note the whorl of fibrous tissue and the perifocal chronic inflammation with Langhans' giant cells $\times 130$ (2) An enlargement of the area on the left upper part of part 1, showing a typical Langhans' giant cell $\times 400$

The pericardium contained 200 to 300 cc of straw-colored fluid. There were several atheromatous plaques in the transverse portion of the aorta.

The heart was 4 cm to the right border of the sternum and weighed 450 gm. It measured 18 by 15 cm. The right auricle was dilated and filled with blood. The wall of the right ventricle was 4 mm in thickness, and the wall of the left 20 mm. The valves were normal except that there was a slight thickening and slight calcification of the aortic and mitral valves. The left ventricular wall was markedly hypertrophied. The interventricular septum was thickened. The musculature was red-brown.

The left lung weighed 675 gm. The pleura was shiny, moist and mottled with grayish areas. There was no evidence of adhesions. There were several black calcified hilum lymph nodes and a grayish mucopurulent secretion in the bronchi.

The right lung weighed 620 gm. The superior lobe was markedly contracted. There was a nodular, firm middle lobe, contracted and fibrotic. Along the mediastinal borders of the right lower lobe were several blebs. There was crepitation of the lower lobe. The upper lobes were firm and noncrepitant. There was a cavity 2 by 1 by 1 cm, surrounded by a markedly fibrotic capsule.

The spleen weighed 115 gm and appeared normal. The left kidney weighed 115 gm, was markedly sclerotic, and the capsule was adherent to the cortex which was gray-brown and 8 mm in depth. The right kidney weighed 145 gm, was pale red and firm with an adherent capsule. The cortex was 6 mm in depth. The liver weighed 1650 gm, was pale mottled reddish-brown. It had sharp borders, and on section was a pale purplish-gray.

All other organs and tissues were essentially normal.

The organs were sent to Dr. Kirschbaum of the Cook County Hospital, Chicago, for diagnosis, and he kindly sent sections and lung tissue to us for study.

Lymph Nodes Section 1. There were small foci of fibrous tissue throughout, about two-thirds of the section. The foci appeared to have formed in the germinal centers of the lymph nodes. They were made up of several broad bands of fibrous tissue coiled in the focus, and sometimes several of these were grouped together. The number of fibers varied up to a large number in which instances they formed fibrotic nodules. Around them were varying amounts of lymphoid tissue in which were situated a few giant cells in different stages of evolution from early monocytic clusters to large disintegrating forms. The architecture of the node was badly deranged. No pigment was present.

Section 2. There was much less fibrosis, but the architecture was deranged throughout. Beneath the capsule on one side there were patches of fibrosis as observed in the first section. In other parts the capillary walls were partly hyalinized, and there were smaller and earlier foci of fibrous tissue with an occasional early giant cell. The lymphoid cells were greatly diminished in numbers. There was no pigment in this node.

Section 3. There was much black pigment present indicating relationship to the bronchi. There was one small fibrotic nodule 1 mm in diameter which resembled a tubercle that had become fibrotic but not caseous. It was composed of solid nodules of fibrous tissue filling up nearly all the node, leaving practically no lymphoid or germinal elements. There were a few atypical giant cells present.

Lung Parenchyma Section 1. The sections were all badly torn but the architecture was fairly normal. The alveoli were not greatly distended and their walls were not overly thickened. Around some of the smaller vessels and beneath the pleura were small fibroid plaques of fibrous tissue that were not densely hyalinized. Outside of some of these smaller plaques was an occasional giant cell. In one or two places throughout the section were much larger areas of fibrosis. The fibrils were not especially arranged in any constant form. The pleura was thickened and there were

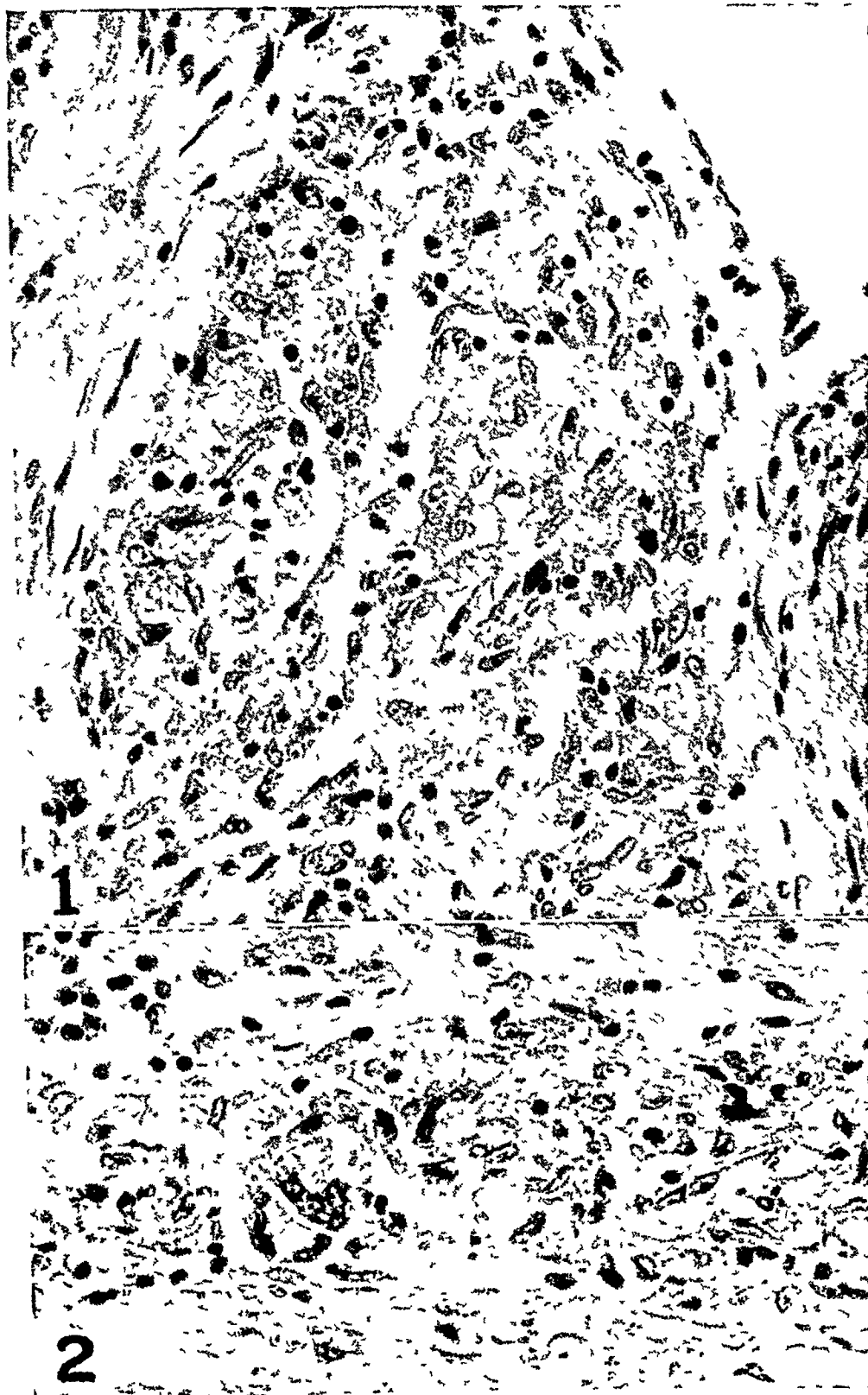


FIG 5 (1 and 2) Photomicrographs of the early lesion in the lung parenchyma revealing monocytes becoming arranged into atypical giant cells $\times 400$

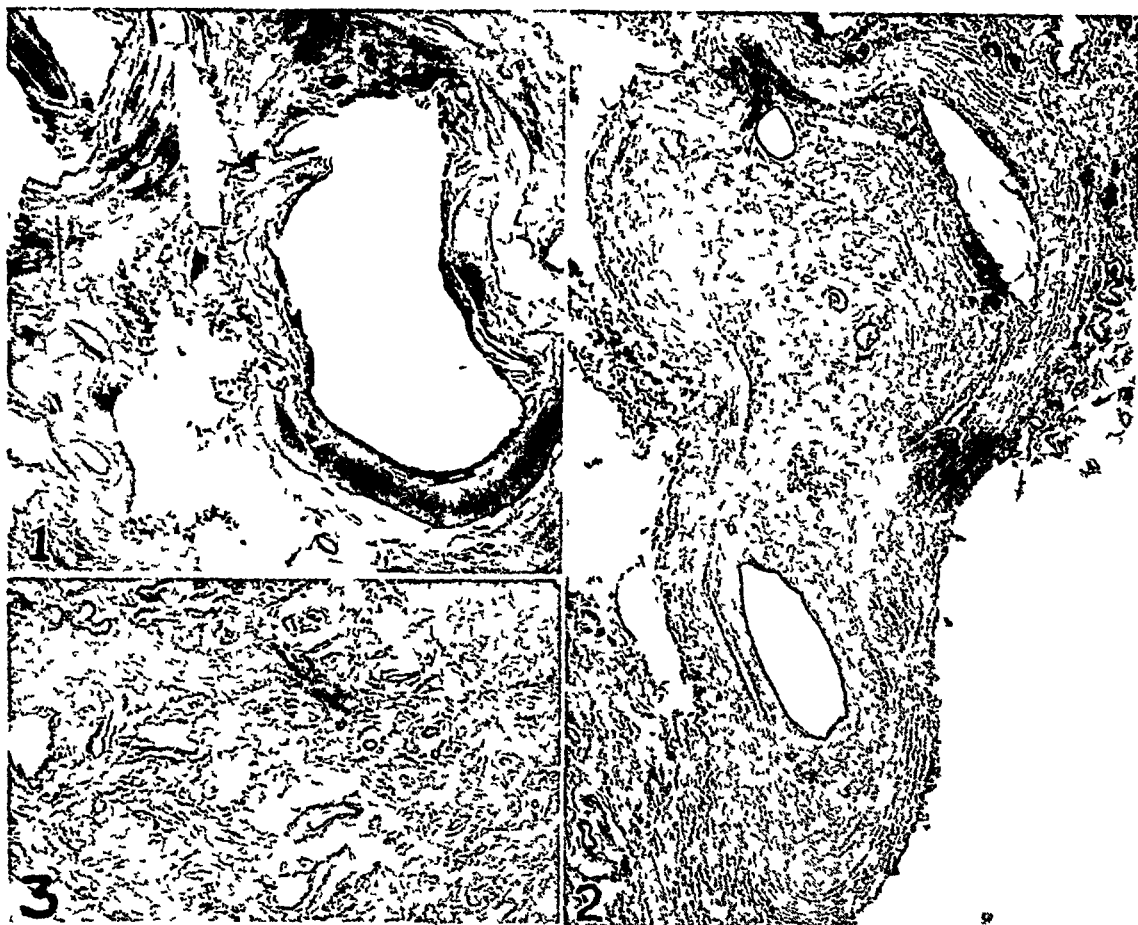


FIG 6 (1) A low power photomicrograph of the lung hilum across a large bronchus revealing a large pulmonary artery undergoing closure by an endarteritis $\times 85$ (2) An enlargement of the artery shown in part 1 $\times 35$ (3) The atelectatic lung tissue $\times 85$

plaques of fibrosis occasionally along the pleura, some of which followed down some of the blood vessels. Certain alveoli were filled with serous exudate.

Section 2 Another section of lung tissue was made up of alveoli that had undergone extensive atelectasis. Practically no normal alveoli could be found. Many of the smaller arteries were completely obliterated by endarteritis. Much brown pigment was scattered throughout. Beneath the pleura in one or two places heavy tortuous masses of fibrous tissue dipped into the parenchyma. The vessels not only showed fibrosis within the lumen but a surrounding zone of periarteritis.

Section 3 This was a similar section with almost complete fibrosis. There was an occasional dilated bronchiole. Much black pigment and heavy bands of fibrous tissue were seen in all parts of the sections surrounding practically all of the vascular and bronchial structures. On one side there was a dense nodule of fibrous tissue that had the appearance of an old fibrotic tubercle. There was no caseation, but much pigment was present. The lesions in this section were apparently older than in any other of those examined.

Section 4 This section revealed bronchi some of which were undergoing dilatation while some were completely obliterated by fibrous contraction. The mucosa of these showed only a few disintegrated goblet cells remaining. The lumen was practically gone. There was heavy fibrous tissue present throughout.

Section 5 A section near the margin of the lung revealed a heavy marginal fibrous layer which at various points along the pleura dipped into the lung structure. There were heavy fibrous bands which followed the arteries toward the hilum. Some of the smaller arterial capillaries were surrounded by rings of heavy fibrous tissue. There were zones of cellular infiltrate bordering the perivascular fibrous tissue. In such zones were numerous irregular giant cells, some composed of three or four pinched nuclei in a bed of lymphoid tissue, while others were complete horse-shoes or circles. Most of them were irregular and imperfect but nevertheless were definitely the Langhans' type of giant cells. Some of the smaller capillaries were surrounded by small and recently formed foci of lymphoid structures in which were many monocyctic cells that were just beginning to suggest the formation of giant cells.

Hilum Section 1 Cross section of a larger bronchus revealed a marked amount of surrounding fibrous tissue localized especially about the arteries. One of the main arteries contained what appeared to be an old thrombus that had become organized and recanalized by two or three small vessels. It was possible, however, that the occlusion was due to a progressive endarteritis.

Section 2 Another pulmonary section of a bronchus revealed another large artery that had become completely obliterated, only one or two very small capillaries being present in the lumen. The peribronchial and periarterial regions were composed of dense fibrous tissue in which there were numerous capillaries containing blood cells.

DISCUSSION AND CONCLUSIONS

In spite of a sketchy history the postmortem evidence of the lung and lymph nodes was sufficient to warrant the opinion that the patient suffered from a systemic disease corresponding to the *benign lymphogranulomatosis of Schaumann*. Death was due to destruction of lung tissue by the lesions of sarcoid as well as to an endarteritis of some of the main branches of the pulmonary artery, leading to cardiac failure. The disease in this instance was apparently healed or healing at the time the heart failed.

The pulmonary vascular obstruction probably led to symptoms of Ayerza's disease. While the heart was enlarged to twice its normal size and the aortic and mitral valves were thickened, the changes were probably secondary and not due to the general disease.

No skin lesions were ever reported and no lesions other than those of the lungs and hilum lymph nodes were found. No acid-fast bacilli were ever found and no caseation was present anywhere in the postmortem material.

This case, therefore, bears out Schaumann's contention that the disease may come on silently, without external lesions, and that it is perhaps first and predominantly a lymph node disease, later involving certain other organs and tissues. The facts also reveal that the process may be a fatal disease in spite of the paucity of symptoms and generally benign character of the usual case.

REFERENCES

- 1 BESNIER, E. Lupus pernio de la face, *Ann de dermatol*, 1889, x, 333
- 2 BOECK, C. Multiple benign sarcoid of the skin, *Jr Cut and Genito-Urin Dis*, 1899, vxii, 543
- 3 SCHAUMANN, J. Étude sur le lupus pernio et ses rapports avec les sarcoides et la tuberculose, *Ann de dermatol*, 1916, vi, 357
- 4 PAUTRIER, L. M. Comment doit se poser la question des sarcoides, *Bull Soc. franc. de Derm et Syph*, 1934, xli, 1002 and 1348

- 5 TILLGREN, J Schaumann's disease (lymphogranulomatosis), Acta med Scand, 1937, **xciii**, 189
- 6 KIENBOCK, R Zur radiographischen Anatomie und Klinik der syphilitischen Knochen-
erkrankungen an Extremitäten, Ztschr f Heilk, 1902, **xliii**, 130
- 7 KREIBICH, K Über Lupus pernio, Arch f Derm, 1904, **lxxi**, 3
- 8 BLOCH, B Beitrag zur Kenntnis des Lupus pernio, Monatsh f prakt Derm, 1907, **xiv**,
177
- 9 RIEDER, H Über Kombination von chronischer Osteomyelitis (Spina ventosa) mit Lupus
pernio, Fortschr a d Geb d Roentgenstr, 1910, **xv**, 125
- 10 JUNGling, O Ostitis tuberculosa multiplex cystica, Fortschr a d Geb d Roentgenstr,
1919-1921, **xxvii**, 375
- 11 SCHAUmann, J Lymphogranulomatosis benigna, Brit Jr Dermat and Syph, 1924,
xxxiv, 515
- 12 DARIER, J Sur la nature et la pathogénie des tuberculides et sarcoides, Schweiz med
Wchnschr, 1929, **x**, 1209
- 13 PAUTRIER, L M Sarcoides de Boeck généralisées, Bull Soc franc Derm, 1933, **xl**,
1540
- 14 GOUGEROT, H, Sarcoides par corps étrangers, Bull Soc franc Dermat, 1934, **xli**, 1370
- 15 KISSMEYER, A La maladie de Boeck, Paris, 1932
- 16 KUZNITZKY, E, and BITTORF, A Boeck'sches Sarkoid mit Beteiligung innerer Organe,
München med Wchnschr, 1915, **lxii**, 1349
- 17 KYRLE, J Die Anfangsstadien des Boeck'schen Sarkoids, Beitrag zur Frage der Aetio-
logie dieser Dermatoze, Arch f Derm, 1921, **cxvxi**, 33
- 18 MYLIUS, K, and SCHURMANN, P Universelle sklerosierende Tuberkulose, grosszellige
Hyperplasie und besonderer Form atypischen Tuberkulose, Beitr z Klin d Tuberk,
1929, **lxxiii**, 166
- 19 PINNER, M Noncaseating tuberculosis, Am Rev Tuberc, 1938, **xxxvii**, 690
- 20 SALVESON, H A The sarcoid of Boeck, a disease of importance to internal medicine,
Acta med Scand, 1935, **lxxxvi**, 127
- 21 SPENCER, J, and WARREN, S Boeck's sarcoid, a report of case with clinical diagnosis
confirmed at autopsy, Arch Int Med, 1938, **lxii**, 285

MICROCOCOCCUS TETRAGENUS MENINGITIS; REPORT OF A CASE AND REVIEW OF THE LITERATURE *

By JOHN E LEACH, M D and FRED G MEDINGER, M D,
New York, N Y

THAT *Micrococcus tetragenus* infections are rare is evidenced by the fact that relatively few cases have been reported in the American literature, and that Reimann, reviewing the foreign journals up until 1935, recorded a total of only 170 cases. During the past five years three cases^{2, 3, 4} have been reported in American journals and an equally small number from Europe. The infrequency of the infection is further shown by the fact that all the reports are concerned with one to three cases with the exception of two mild separate epidemics¹ affecting 70 soldiers during the World War, 1914-1919. The first reports of *Micrococcus tetragenus* infection in this country were made by Griewe in 1899 and Steele in 1914.

The *Micrococcus tetragenus*, a gram-positive organism occurring in tetrads first described by Koch and Gaffky in 1881 and often called by the latter's name

* Received for publication October 18, 1940

is found as a normal saprophyte in the mouth, nose and throat, and occasionally in pulmonary tuberculous or abscess cavities Jakowski⁵ in 1886 was the first to report on its pathogenicity and low powers of virulence The organism has a predilection for serous membranes, producing inflammation and suppuration With lowered resistance of the patient it tends to invade the lymphatics or blood stream and produces abscesses in remote serous cavities and parenchymatous organs From a clinico-pathological aspect, the close resemblance to staphylococcal infections is apparent and because of the close bacteriologic resemblance to staphylococcus the diagnosis may often be difficult

The infection is most common in infancy and among virile young adults The sex ratio is generally about three males to one female Sore throat and respiratory infections, anemia, typhoid fever, undulant fever, streptococcal infections, alcoholism and prolonged heat exhaustion have been noted as important predisposing factors lowering the resistance of the patient The reason for the low incidence among the aged and debilitated cannot be explained The onset of the disease is usually abrupt and in cases with septicemia, a sharp chill precedes the fever of a remittent type, ranging from normal to 106° F Although only a few of the reported cases have shown positive blood cultures, it is reasonable to assume that the metastatic abscesses which may occur in any organ, particularly in serous cavities, are due to blood stream invasion Those areas most frequently reported as sites of localization are nasal sinuses, lungs, pleura, pericardium and endocardium, middle ear, peritoneum, joints, fallopian tubes, endometrium, kidneys, bladder, colon and least frequently the meninges The symptoms and physical findings are those of infection with suppurative inflammation at one or several sites of localization Among Reimann's collected series, patients with fulminating infections have died within seven to ten days and in others the disease has run a course as long as seven months In cases with septicemia the mortality rate is about 50 per cent Since there are no characteristic signs of *Micrococcus tetragenus* infection and specific agglutinins in the patient's serum are often of low titer or absent, recovery and growth of the organism from the infected tissue are the only positive method of diagnosis

This report is concerned with one case of *Micrococcus tetragenus* meningitis with septicemia, which terminated fatally following the added complications of pneumococcal and streptococcal meningitis This case is of interest not only because of its rarity and unusual clinical course but also because it is one of the first to be evaluated for the effect of the sulfonamide derivative drugs on the course of the infection In 1939, Criscietello³ reported the first case of *Micrococcus tetragenus* meningitis treated by sulfanilamide with recovery

A survey of all the literature reveals 14 previously reported cases of *Micrococcus tetragenus* meningitis, the first by Bezancon and Lepage⁶ from Paris in 1898, the remainder by Boettinger⁷, Pende⁸, Vincent⁹, Perfetti¹⁰, Ramond¹¹, two cases, Leschke¹², Griewe¹³, Bonnanno¹⁴, Blum¹⁵, Reimann¹, McGowan², and Criscietello³ The salient features of these cases are shown in table 1

CASE REPORT

G M, aged 50, white, married housewife, following a right sided rhinorrhea of several months' duration was found in June 1939 to have a carcinoma of the right antrum which on biopsy showed epidermoid carcinoma, Grade II A Caldwell-Luc antrotomy with drainage was done and this was followed during the next four months

TABLE I

Case	Sex	Age	Predisposing Factor	Onset	Duration	Clinical Signs	Blood Culture	Spinal Fluid Culture	Agglutinins	Treatment	End Result	Other Findings
Bezancon and LePage 1898	F	?	Puerperal sepsis	Epileptic attacks	1 Mo	Hemiplegia, coma and fever					Fatal P M - Meningitis Cult <i>Micro tetra</i>	
Griewe and Mitchell 1899	M	35		Sudden	3 Wk	Meningitis		Pos			Fatal	None
Boettinger and Malloirel 1906	M	58	Pleurisy	Sudden	5 Da	Meningitis		Pos		Lumbar puncture	Fatal p m	Pleura culture pos for <i>Micro tetra</i>
Pende 1908	F	48	None	Sudden	25 Da	Meningitis		Pos		Lumbar puncture	Fatal	None
Vincent 1908	F	?	None	Gradual	10 Da	Cerebral		Pos		Lumbar puncture	Recovered	None
Ramond and Resibois 1915	?	?	None	Sudden	Sev Da	Respiratory vaso-motor		Pos		Lumbar punct, injection of colloidal gold	Recovered	None
Ramond and Resibois 1915	?	?	None	Sudden	Sev Da	Vomiting		Pos		Lumbar punct, injection of colloidal gold	Recovered	None

TABLE I (Continued)

Case	Sex	Age	Predisposing Factor	Onset	Duration	Clinical Signs	Blood Culture	Spinal Fluid Culture	Agglutinins	Treatment	End Result	Other Findings
Perfetti and Monziols 1918	M	?	Pyoderma	Sudden	6 Wk	Mixed localization	Pos	Pos		Lumbar puncture	Fatal p m	Peritonitis, pericarditis, renal abscesses, bone abscesses
Leschke 1919	M	23	Sore throat	Sudden	7 Da	Meningitis, arthritis	Pos	Pos		Lumbar puncture	Fatal	None
Blum 1923	M	15	None	Sudden	3½ Mo	Meningitis	Pos	Pos	1/2000	Lumbar punct , autogenous vaccine	Recovered	Nephritis, cystitis
Bonnano 1931	M	28	None	Sudden	4 Wk		Neg	Pos			Recovered	None
Reimann 1935	M	46	Sore throat	Sudden	7 Wk	Meningitis	Pos	Pos		Lumbar puncture	Recovered	Joints, prostate
McGowan and Kinsner 1939	M	40	Heat exhaustion	Sudden	5 Wk		Pos	Pos	Pres	Lumbar punct , meningococcus serum	Recovered	?
Crisietello 1939	M	18	None	Sudden	3 Wk			Pos		Lumbar punct , sulfanilamide	Recovered	None
Authors'	F	50	Post-oper sinusitis	Sudden	6 Wk		Pos	Pos		Lumbar punct , sulfanilamide drugs	Fatal p m	None

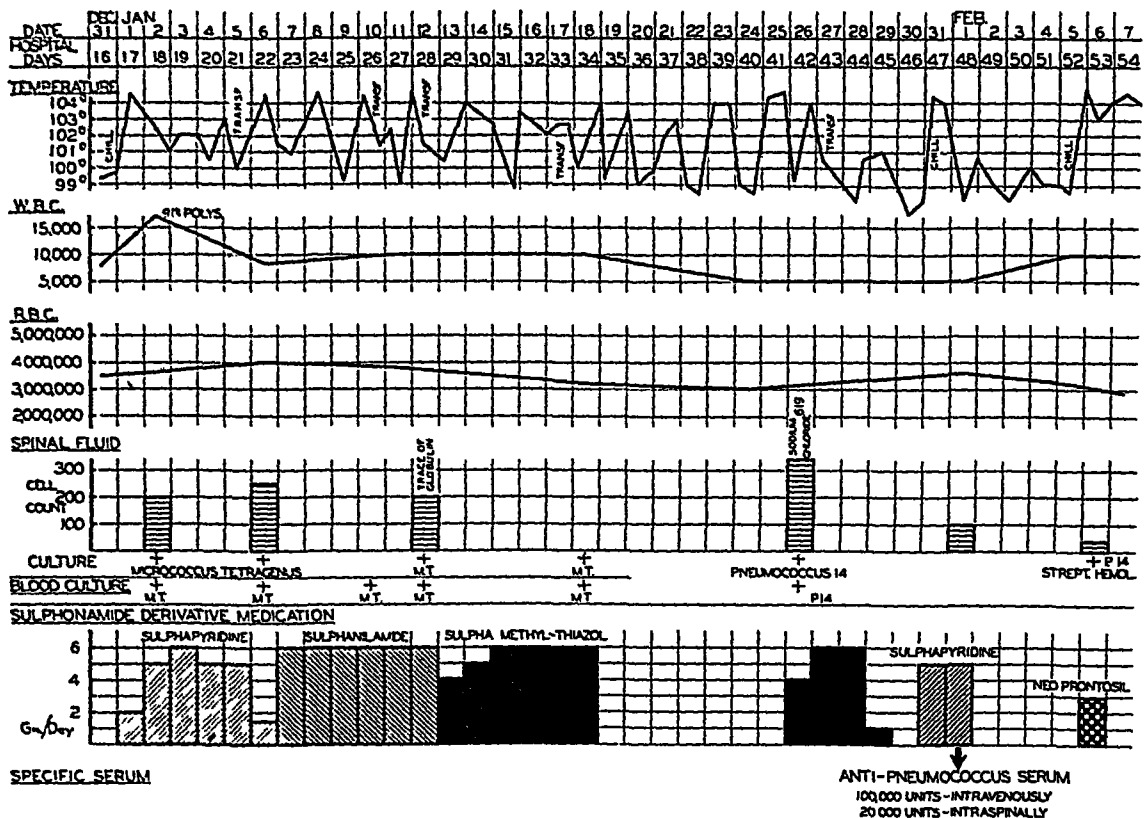


FIG 1

by several courses of external and peroral roentgen-ray therapy plus radon seed implantation into the antrum. Because of the extensive involvement of the floor of the orbit by cancer and marked proptosis of the eye, a cautery excision of the roof of the antrum was performed on 12/15/39 followed in one week by exenteration of the orbit. Except for low grade fever with toxicity, the post-operative course was uneventful for two weeks.

On 1/1/40 following a sharp chill the patient developed a fever of 104° F and became irrational. There was moderate neck rigidity, exaggerated deep tendon reflexes and positive Kernig and Babinski signs. At the lung bases there were inconclusive signs of an early pneumonitis. Following a lumbar puncture showing turbid fluid under normal pressure, a presumptive diagnosis of pneumococcic meningitis was made and a course of sulfapyridine medication, one gram every four hours, was begun.

On 1/2/40 the blood and spinal cultures were reported as showing a pure growth of an atypical coccus which after several days of study proved to be *Micrococcus tetragenus*. The medication was then changed to sulfanilamide but signs of septicemia and meningitis continued unabated and at the end of 12 days blood and spinal fluid cultures were still positive for *Micrococcus tetragenus*. The antral cavity was carefully debrided and irrigated several times daily with Dakin's and sulfanilamide solutions. About the optic foramen and base of the orbital defect there was considerable infection, with necrotic bone fragments and slough. On several occasions, gentle debridement of the slough was followed by an immediate chill and fever which led us to believe that this area was the focus of infection and that by eradication of this focus the source of the meningitis would be removed.

On 1/12/40 the medication was changed to 6 grams of sulfa-methyl thiazole daily but after six days spinal fluid culture was still positive. Although the patient was mentally alert and showed no physical signs of meningitis during the next two weeks

fever persisted and repeated lumbar punctures every three to four days showed slight turbidity. All specimens were positive for *Micrococcus tetragenus*.

On 1/31/40 following a severe chill the signs of meningitis recurred with headache, fever and neck rigidity. Cultures of the blood and of a cloudy spinal fluid showed Pneumococcus type 14. The patient was then given 120,000 units of anti-pneumococcus type 14 serum intravenously with 20,000 units intraspinally and intravenous injections of 5 grams of sodium sulfapyridine on two successive days. Immediately the temperature returned to normal. There was a clearing of the sensorium, signs of meningitis rapidly subsided and for the first time the blood and spinal fluid cultures were negative.

For three days the course was normal. Then she had a sharp chill followed by a temperature of 105° with recurrent signs of meningitis. Lumbar puncture gave a slightly turbid fluid which on culture showed a predominant growth of hemolytic streptococci and a few colonies of Pneumococcus type 14. Because of severe nausea and vomiting 20 c.c. of 5 per cent neoprontosil was administered intravenously and intramuscularly but the patient failed to respond to medication and supportive treatment and died on 2/7/40.

Postmortem Findings Gross and microscopic examination of the nasal sinuses and cervical lymph nodes showed no residual carcinoma. On removing the brain, the dura and meninges were markedly inflamed and thickened due to congestion and edema. Two distinct types of meningitis were apparent from the type of the cerebral exudate present. Over the frontal lobes the exudate was a thin glaze brownish fluid. Extending posteriorly from the Sylvian fissures and on the inferior surface of the brain was a thick yellow-green purulent exudate. On opening the right sphenoid sinus 5 c.c. of thick greenish pus under pressure drained into the cranial cavity. Purulent material was easily expressed from about both optic tracts. The roof of the right sphenoid sinus was necrotic and the base of the hypophysis was surrounded by purulent exudate. The apparent route of migration of the infection was from the nasopharynx or orbital cavity to the sphenoid sinus and thence along the optic tracts and through the roof of the sphenoid sinus to the hypophysis and meninges. Section of the brain showed no abscesses. Microscopic examination confirmed the gross findings. Culture of the meninges showed Pneumococcus, unfortunately no cultures were taken from the sphenoid sinus.

The diagnosis of *Micrococcus tetragenus* meningitis is primarily a bacteriologic problem. Since this organism on smear may be confused with staphylococcus or meningococcus, the diagnosis depends entirely on recognition of the organism's cultural peculiarities. From previous case studies it is seen that the clinical characteristics of this type of meningitis are with few variations the same as seen in meningococcal meningitis. Significant in the differential diagnosis is the presence of all cocci in an extracellular position and the rapid growth of the *Micrococcus tetragenus* on culture. However, these are not conclusive.

The peculiar properties of bacterial dissociation or pleomorphism exhibited by this organism are its most characteristic feature as is demonstrated by studies in this case and also by Reimann¹ and McGowan and Kinsner². Initial blood and spinal fluid cultures gave a pure growth of gram-positive cocci occurring predominantly in tetrads, growing in delicate translucent colonies which on standing 48 to 60 hours became opaque white and yellow. Later cultures gave a growth of only scattered white colonies in which the organisms appeared in single diploid and clump formations, showed marked variation in size and stained mainly gram-negative. On first thought, this was believed to be due to bacterial attenuation resulting from the drug therapy, but after reviewing the studies of Reimann¹, 16, 17

this was accepted as being characteristic of the bacteria. About some of the older colonies on blood agar, a greenish color with slight hemolysis was noted. The organisms characteristically failed to liquefy gelatin and fermented none of the sugars.

The few immunologic studies carried out in cases with this infection demonstrate that the production of antibodies in the human is variable and inconstant. In two cases reported by Kiamar¹⁸ and Meltzer¹⁹ agglutinin titers as high as 1-500 and 1-640 were reported. Blum's case of meningitis¹⁵ with septicemia and cystitis showed agglutinin titers varying from 1-300 to 1-2000. However, in cases reported by Von Oppenheim²⁰ and Reimann¹ no specific agglutinins were found in the patient's blood and intradermal injection of a prepared vaccine failed to produce a reaction. Studies by McGowan and Kinsner² showed that the bacterial suspensions in low titer were agglutinated by polyvalent anti-meningococcal serum but showed no reaction with the patient's own serum. In this case bacterial suspensions in standard dilutions mixed with the patient's serum failed to show any agglutination or precipitation both by microscopic and macroscopic technique.

McGowan has found the *Micrococcus tetragenus* to be non-pathogenic for animals, but according to Reimann's immunologic studies in animals^{1, 16, 17} each bacterial variant evokes specific agglutinins and precipitins in low titer. Animal studies throw no light on the variable immunologic responses seen in humans. However, a review of cases suggests that antibodies appear in the blood stream if the infection is prolonged for several months.

The value of sulfanilamide drug therapy for *Micrococcus tetragenus* infections is questionable. In Criscietello's case of meningitis⁸ treated by sulfanilamide with recovery, the one blood culture taken one week after therapy was begun was negative and therefore inconclusive. In this instance, septicemia persisted in the presence of an undrained purulent sphenoid sinusitis so that one is unable to estimate accurately the bacteriostatic effect of the drug therapy, but it may correspond roughly to the weak bacteriostatic effect of the drug noted by Long and Bliss²¹ on in vitro cultures of *Micrococcus tetragenus*. It is interesting to observe that the administration of anti-pneumococcus serum after 33 days produced the first negative blood and spinal fluid cultures along with complete remission from symptoms. Since effective antibody formation has been demonstrated in a few cases of long duration, the autogenous vaccine therapy used in three cases of generalized infection with septicemia with recovery reported in 1920 by Ludke²² impresses one as rational specific therapy for this disease, particularly in the low grade chronic form. It is doubtful that it would offer help for the acute fulminating type of infection.

The distinctive feature of this case was the development of infection in a postoperative orbital and antral defect with the development of an unsuspected sphenoid sinusitis. The organisms spread either by the blood stream or by lymphatics along optic nerves and through the roof of the sphenoid and infected the meninges. Previous to the development of the streptococcal meningitis it was our clinical impression that this patient was steadily improving and would make a full recovery. The autopsy findings clearly show (1) the pathogenesis of the successive meningeal infections, (2) the reason for failure to improve after intensive sulfanilamide therapy and (3) the need for careful search and elimination of any focus of infection. The presence of some purulent and necrotic

slough in the base of the orbital defect which when debrided was followed by fever and chill, made us believe that this was the only focus of infection producing the meningitis. If the hidden focus of bacteria in the sphenoid sinus had been discovered and drained early it is reasonable to assume that the terminal pneumococcic and streptococcic meningitis would have been prevented and the patient would have recovered.

BIBLIOGRAPHY

- 1 REIMANN, H A *Micrococcus tetragenus* infection, Jr Clin Invest, 1935, xiv, 311-319
- 2 MCGOWAN, T S, and KINSNER, P A review of meningitis due to *Micrococcus tetragenus*, Arch Int Med, 1939, lxiv, 15-25
- 3 CRISCITELLO, M, JR Meningitis due to *Micrococcus tetragenus*, New England Jr Med, 1939, lxxxix, 383-385
- 4 BLACKBURN, J H *Micrococcus tetragenus* as surgical complication, South Surg, 1937, vi, 422-426
- 5 JAKOWSKI Cited by von Oppenheim²⁰
- 6 BEZANCON, F, and LEPAGE, C Ménigite suppurative localisé due au *Micrococcus tetragenus*, Bull et mem Soc méd des hôp de Paris, 1898, xv, 36-40
- 7 BOETTINGER, M M, and MALLOIZEL Septicémie a tetragenes, Bull et mem Soc méd des hôp de Paris, 1906, xxiii, 123-129
- 8 PENDE Cited by Blum, L¹⁵
- 9 VINCENT Quoted by Blum, L¹⁵
- 10 PERFETTI, M, and MONZIOLS, M Complications multiples au cours d'une septicémie a tetragenes d'origine cutanée, Bull et mem Soc med des hôp de Paris, 1918, xlii, 768-772
- 11 RAMOND, F, and RESIBOIS, A A propos du traitement des méningites cerebrospinales, Progres Med, 1914, xxx, 438-445
- 12 LESCHKE, E Cited by Reimann, H A¹
- 13 GRIEWE, J E, FACKLER, G A, MITCHELL, E W, and HELLMAN, F F Meningitis with the tetragenus micrococcus as probable cause, Philadelphia Month Med Jr, 1899, i, 528-531
- 14 BONNANO, A M Cited by Reimann, H A¹
- 15 BLUM, L, VAUCHER, E, and KARBIENER Les meningites a tétragènes, Rev de Med, 1923, xi, 577-593
- 16 REIMANN, H A The significance of bacterial variation, Jr Bact, 1937, xxxiii, 513-523
- 17 REIMANN, H A *Micrococcus tetragenus* infection, Jr Bact, 1936, xxxi, 385-421
- 18 KRAMAR, E Cited by Reimann¹
- 19 MELTZER, O Ueber den *Micrococcus tetragenus* bei Septikämien und Mischinfektionen, München med Wchnschr, 1910, lvii, 743-744
- 20 VON OPPENHEIM, E Three cases illustrating the treatment of septicemia by vaccine therapy, Proc Roy Soc Med, Clin Sect, 1909, ii, 159-167
- 21 LONG, P, and BLISS, E Clinical use of sulphanilamide and sulphapyridine and allied compounds, 1939, MacMillan
- 22 LUDKE, H Ueber Tetragenussepsis, München med Wchnschr, 1920, lxvii, 454-455

EDITORIAL

EDEMA

THE basic etiologic causes of the production of generalized edema are much better understood than even ten or fifteen years ago and the treatment administered is on an improved physiologic basis. By a differential diagnosis we are able to determine more accurately the cause of the edema and thereby institute a more logical therapeutic program.

When edema is present, a number of possible conditions must be considered and after a careful analysis of the history and the physical and laboratory findings an accurate diagnosis is possible in most cases. Conditions commonly producing edema are glomerulonephritis, both the acute and chronic stages, and nephritis associated with the nephrotic syndrome. Cardiac disease with congestive failure must be considered as an etiologic condition in edema and frequently both cardiac disease and nephritis coexist. Other conditions not so common, but which must be considered as possible causes of the edema, are hepatic cirrhosis, polyserositis, myxedema, malignant growths and lymphedema. Space will not permit a discussion of the differential diagnosis of these various conditions but suffice it to say that when the correct diagnosis is made the treatment is usually definite.

Perhaps the most classical type of edema and the type that usually responds most satisfactorily is that produced by chronic glomerulonephritis with the nephrotic syndrome. In these cases the renal function per se is usually good and the edema is due largely to enormous loss of protein in the urine, a lowered serum protein and a lowered colloidal osmotic pressure resulting in retention of salt and water in the tissues. The treatment is directed toward correcting this situation by restoring the physical and electrolytic balance in the body. The patient is given a high protein, salt-free diet which is low in fluid. This provides for 100 to 125 gm of protein a day and 800 to 1,000 c c of fluid. Potassium nitrate, 6 to 12 gm daily, is a satisfactory diuretic salt and one that does not disturb appreciably the acid base equilibrium. As a "physiologic splint" to increase temporarily the colloidal osmotic pressure of the blood until serum protein is formed as fast as it is lost in the urine, from 90 to 150 gm of acacia can be given. As a rule 500 c c of 6 per cent solution of acacia in 0.06 per cent solution of sodium chloride are given intravenously on successive or alternate days for three to five injections or until the concentration of acacia in the blood is about 2 per cent. This, in addition to the 3 to 5 per cent concentration of protein in the serum in these cases produces a sufficient colloidal osmotic pressure in most instances to result in adequate diuresis and gradual elimination of fluid and salt from the body. Even when the patient is taking a salt-free diet, as much as 24 gm of salt have been eliminated in the urine in a day. It is not un-

common to observe an output of from 3 to 5 liters of urine in twenty-four hours. It is seldom necessary to resort to mercurial diuretics with this program.

Of late considerable attention has been directed to the use of dried plasma and to lyophil serum in preference to acacia. Lyophil serum seems more toxic than solution of dried plasma. Rarely does either a solution of dried plasma or one of acacia cause unpleasant reactions. Solution of acacia has the advantage of being more economical, easier to obtain and prepare and remains in the blood stream a longer time. Reactions from acacia seldom occur if a pure solution is used. Blood transfusions present similar problems and in addition necessitate careful grouping and are associated with occasional reactions.

In cases of acute nephritis in which oliguria exists and in which the serum protein is still normal or nearly normal it is well to eliminate salt from the diet. From 50 to 60 gm of protein a day are given. Five hundred cubic centimeters of 20 per cent solution of glucose or 1,000 c c of a 10 per cent solution with an ampule of aminophylline ($3\frac{3}{4}$ grains or 0.25 gm) is usually helpful as a mild diuretic. Potassium nitrate may be given in these cases but it is not advisable to use mercurial diuretics unless a diuresis is already established.

In cases of cardiac disease with congestive failure it is highly important to rid the body of the offending substance, namely, the edema fluid, as frequently the lungs, liver and other tissues of the body are engorged with water. In cases of edema caused by cardiac failure, mercurial diuretics offer quicker and more complete relief in ridding the body of fluid than any other diuretic. They should not be given, however, in the presence of renal failure with uremia. The xanthine group offers effective therapeutic aid and in combination with the mercurial diuretics adds materially to our resources. Potassium nitrate also is a diuretic aid in these cases and can be employed effectively. From 500 to 1,000 c c of a 10 per cent solution of glucose with an ampule of aminophylline ($3\frac{3}{4}$ grains or 0.25 gm) is effective in many cases. It should be given slowly and if symptoms of pulmonary congestion occur, the injection should be discontinued. By the addition of an ampule of aminophylline ($3\frac{3}{4}$ grains or 0.25 gm) to the solution reactions are materially decreased in frequency and degree.

Digitalis has for many years held a prominent place in the treatment of congestive failure, especially in the long convalescent period. Its action should be closely watched and the physician should always be on guard for symptoms of toxicity, especially in the older individual.

In cases of hepatic cirrhosis excess fluid collects first in the abdominal cavity. Usually paracentesis is necessary repeatedly and the patient may require paracentesis once or twice a week. Usually hypoproteinemia does not exist. However, injections of 500 c c of a 6 per cent solution of acacia in 0.06 per cent solution of sodium chloride have seemed to increase diuresis.

and slow down the accumulation of fluid in the abdominal cavity. A salt-free diet with an intake of 500 to 800 c c of fluid daily is advisable. Potassium nitrate, 6 to 9 gm a day, has some diuretic effect. Operation is not of much value in these cases.

It is a good rule in any case of generalized edema to keep the intake of salt as low as possible, to try to restore the electrolytic and physical balance in the body, to restore as nearly as possible the normal function of the heart and kidneys and to eliminate the excess fluids retained in the body by the therapeutic measures of choice. Therapeutic measures which might produce reactions in the body should be avoided if possible.

M W B

REVIEWS

Clinical Aspects of the Electrocardiogram By HAROLD E. B. PARDEE, M.D. 434 pages, 24 × 16 cm Paul B. Hoeber, Inc., New York 1941 Price, \$5.75

The fourth edition of this book, which has been revised and enlarged, maintains the good standards set by previous editions. It is a comprehensive text on every aspect of clinical electrocardiography, and is strongly recommended to the cardiologist and internist. It can also be read with profit and interest by medical students, physiologists and others interested in electrocardiography. The author has devoted much space to a discussion of the normal and abnormal variations of the electrocardiogram, and even though there is a relative paucity of tracings pictured, it is evident that each is carefully chosen to reveal several deviations. The tracings are, for the most part, distinctly reproduced and each is followed by a brief descriptive analysis of the abnormal details. The author discusses controversial subjects, briefly states his own views, and supports them with statistical data compiled either by himself or other workers in this field.

A definitely worthy feature is the correlation of the clinical significance of axis deviation, abnormal waves and arrhythmias with anatomical, pathological and physiological investigations. This is particularly well done in the discussion of bundle-branch block, myocardial infarction, extrasystoles and heart block. One chapter is devoted to purely clinical features of the arrhythmias with specific reference to their origin, diagnosis and prognosis.

Only recently has there become apparent some unanimity of opinion concerning the evaluation of the different chest leads and the interpretation of their respective abnormal deviations. The author presents the current opinions with reference to these leads. He describes the chest leads and illustrates them with tracings together with each set of normal and abnormal standard leads, thus giving the reader a complete picture of the electrocardiogram. Detailed information is given concerning the nomenclature and terminology recommended by the American Heart Association and the Cardiac Society of Great Britain and Ireland.

The theories of the physiological and mathematical fundamentals are discussed in a chapter which, although very stimulating and instructive, is in places slightly confusing. Appendix I is concerned with methods of determination of electrocardiogram vector directions. The necessary tables and charts are given for their computation.

Each chapter is followed by a current, adequate bibliographical reference list arranged according to the various subjects discussed.

It is gratifying to note that the author's conception of the value of clinical electrocardiography includes a realization that this procedure has the same degree of limitation as any other single method of cardiac examination. This point is illustrated by the following quotations: "The decision as to the interpretation of the electrocardiographic changes must be made on clinical grounds." "The electrocardiogram like any other single feature of the clinical examination is quite insufficient as an isolated fact to afford a basis for a prognosis."

E T L

Williams' Obstetrics A Textbook for the use of Students and Practitioners Eighth edition By HENRICUS J. STANDER, M.D., F.A.C.S. 1401 pages, 25 × 17.5 cm D. Appleton-Century Company, New York 1941 Price, \$10.00

While the traditional form and conservative teaching of "Williams' Obstetrics" have been retained, the author points out that "The book has been almost completely rewritten, with the result that little of the original text remains unaltered." Com-

paring this eighth with the first edition, one finds startling differences in size and text which are the result of progress made in obstetrics during the 38 years intervening between the first and present editions. The first edition appeared in 1903 and contained 845 pages, 630 illustrations, and the index occupied 26 pages. The present edition published this year contains 1401 pages, 925 illustrations on 718 figures, while the index occupies 62 pages. Space in a brief review does not permit the interesting comparison of methods described in the two editions or even a list of new material added since the first appeared.

Since the seventh edition, three new chapters have been added covering the subjects of diseases and abnormalities of the newborn, classification of abnormal and contracted pelvis, and sudden death and maternal mortality. This new edition is full and modern. The average medical student will probably welcome the shortening of the section on embryology. The new classification of the toxemias of pregnancy of the American Committee on Maternal Health has been used, and a new classification of contracted and abnormal pelvis is proposed. Because of the length of this material on the pelvis, it is the opinion of the reviewer that the student will find it rather difficult to assimilate. Roentgen pelvimetry is discussed in detail. Newer operative technics are adequately described, and medical and surgical conditions complicating pregnancy are thoroughly discussed. Proper emphasis has been placed on chemotherapy in the treatment of urinary tract infections as well as in puerperal infection. The chapter dealing with amnesia, analgesia and anesthesia in labor admirably covers this field.

A welcome change from the older editions of this classic text has been the relegation of much of the theoretical considerations to small type. Historical material, while also presented in small type, has been retained and given its proper place.

The type is large, clear and easily readable. There is a large index for this large book. References to the literature, both historical and modern, are given at the end of each chapter. The publishers state that more than half of the illustrations are new. The work is profusely and excellently illustrated with drawings by Elizabeth Brodel, photographs and improved illustrations.

The author is to be congratulated upon the diligent way in which he has preserved the tradition of the work and the thoroughness with which it has been modernized. The resulting book remains one of the outstanding classics, for student and practitioner, in American obstetrics.

J E S

Clinical and Experimental Investigations on the Genital Functions and Their Hormonal Regulation. By BERNHARD ZONDEK. 264 pages. Williams and Wilkins, Baltimore. 1941. Price, \$4.50.

When a man as closely identified with the development of sex physiology as Bernhard Zondek writes a book on the subject it deserves careful study. The introduction clearly states the scope of the material covered as the author's own contributions to the field since 1935. These include work on the natural occurrence of estrogens, the effects of high doses of estrogens, the fate of sex hormones in the organism, and menstrual studies.

For one without a good background in sex physiology this book would be difficult to evaluate. The data are frequently insufficient to warrant the conclusions made, for the work of one man, especially when spread over many problems, is rarely adequate for establishing fundamental principles. Dr Zondek runs into this difficulty particularly in the problems connected with the menstrual cycle, where arguments based on the rat are applied to the human with little consideration of the experimental work done in other laboratories on the monkey. Only a few clinical cases are presented in evidence.

Workers in this country will probably take greatest issue with the terminology. We like to think that the last 10 years have clarified the relations of the prolans to the pituitary principles and proved the identity of pseudomenstruation and menstruation. Zondek's terms synprolan for the pituitary synergist (generally considered in this country to be FSH) and prosylan as prolan plus synprolan imply more knowledge than we possess. According to this system FSH should be called prosylan A, although no one has described a synprolan A.

The work of the author, the content of some 85 published articles, is well summarized and in a convenient form for reference. Many of the ideas are stimulating, especially the author's theory of the mechanism of menstruation.

E B

Bacteriology in Neuropsychiatry By NICHOLAS KOPELOFF, Ph D 316 pages, 15.5 × 23.5 cm Charles C Thomas, Springfield, Ill 1941 Price, \$4.50

The author presents in this volume a survey of the literature relating to the bacteriologic and immunologic phase of neurology and psychiatry. The subject is considered under the following headings: diseases of known etiology with primary involvement of the nervous system, diseases of known etiology with secondary involvement of the nervous system, diseases of unknown etiology involving the central nervous system, and immunology of the central nervous system.

It is of value to have consolidated in a single volume the facts and problems of this extensive subject uncritically presented and interpreted. The book contains an extensive bibliography.

E F C

COLLEGE NEWS NOTES

GIFTS TO THE COLLEGE LIBRARY

We gratefully acknowledge receipt of the following gifts donated to the College Library of Publications by Members

Books

- Dr Benjamin W Black, F A C P , Oakland, Calif —“ Medical Policies and Procedures for the Resident Staff of the Alameda County Hospitals and Clinics ”,
Dr Edgar Hull, F A C P , New Orleans, La —“ Essentials of Electrocardiography ”,
Dr Sidney A Portis, F A C P , Chicago, Ill —“ Diseases of the Digestive System ”,
Dr Isaac Silverman, F A C P , Washington, D C —“ The Psychical Function of the Cerebellum ”,
Dr Edward A Strecker, F A C P , Philadelphia, Pa —“ Practical Clinical Psychiatry ”

Reprints

- Dr Neil D Bue, F A C P , Marlin, Tex —1 reprint,
Rear Admiral Charles S Butler, F A C P , (MC), U S N , Retired, Bristol, Tenn —1 reprint,
Dr Israel Davidsohn (Associate), Chicago, Ill —21 reprints,
Dr Cesar Dominguez, F A C P , Humacao, P R —1 reprint,
Dr. Julius Gottlieb, F A C P , Lewiston, Maine —4 reprints,
Dr Theodore F Hahn, Jr (Associate), DeLand, Fla —4 reprints,
Dr M Coleman Harris, F A C P , New York, N Y —4 reprints,
Dr Oswald F Hedley, F A C P , Bethesda, Md —1 reprint,
Dr Charles Hyman (Associate), Atlantic City, N J —1 reprint,
Dr Everett C Jessup, F A C P , Roslyn, N Y —1 booklet,
Dr Charles J Koerth (Associate), San Antonio, Tex —3 reprints,
Dr Thomas H McGavack, F A C P , New York, N Y —1 reprint,
Dr John H Musser, F A C P , New Orleans, La —20 reprints,
Dr Arthur Dale Nichol (Associate), Cleveland, Ohio —2 reprints,
Dr. Robert C Page (Associate), Mount Vernon, N Y —2 reprints,
Dr Ramon M Suarez, F A C P , San Juan, P R —1 reprint,
Dr Samuel Weiss, F A C P , New York, N Y —1 reprint,
Dr August A Werner, F A C P , St Louis, Mo —6 reprints

SCHEDULE OF EXAMINATIONS BY CERTIFYING BOARDS

The following Boards have announced schedules of their examinations as follows

AMERICAN BOARD OF INTERNAL MEDICINE
William S Middleton, M D , Secretary
1301 University Ave
Madison, Wis

Written Examinations October 20, 1941,
February 16 and October 19, 1942
Oral Examinations St Paul, April, 1942,
in connection with meeting of the
American College of Physicians,
Atlantic City, June, 1942, in connection
with meeting of the American
Medical Association

AMERICAN BOARD OF DERMATOLOGY AND
SYPHILOLOGY
C Guy Lane, M D , Secretary
416 Marlboro St,
Boston, Mass

Written Examination November 3, 1941
Oral Examination December 12-13,
1941

AMERICAN BOARD OF PEDIATRICS
C A Aldrich, M D , Secretary
707 Fullerton Ave
Chicago, Ill

Oral Examination Boston, October 7-8,
1941, in connection with the meeting
of the American Academy of Pedi-
atrics

AMERICAN BOARD OF PSYCHIATRY AND
NEUROLOGY
Walter Freeman, M D , Secretary
1028 Connecticut Ave, N W
Washington, D C

Oral Examination New York, December
19-20, 1941

For further details and application forms communicate with the respective secretaries

The Administrator of Veterans Affairs has established a Neuropsychiatric Research Unit at the Veterans Administration Facility, Northport, L I, N Y The unit will operate as an integral part of the Medical and Hospital Service under the direction of Dr Charles M Griffith, F A C P, Medical Director, and under the immediate supervision of Dr Hugo Mella, F A C P, Chief, Postgraduate Instruction and Medical Research Division, Medical and Hospital Service, Washington, D C

This unit will conduct clinical and laboratory research in connection with neuropsychiatric disabilities found among veterans An effort will also be made to standardize diagnostic and therapeutic methods used in connection with the management of neuropsychiatric diseases and, from time to time, the personnel of the unit will be engaged in teaching modern concepts of neurology, psychiatry and neuropathology to medical officers of the Veterans Administration detailed for this purpose

The National Gastroenterological Association has announced that its 7th Annual Spring Convention will be held in New York, N Y , June 3-5, 1942

The Pittsburgh Pediatric Society held its regular meeting in connection with a "pediatric clinic day" at the Windber Hospital, Windber, Pa , June 25, 1941 Dr Hyman A Slesinger, F A C P, Windber, spoke on "Allergy in Childhood," and Dr Elwood Stitzel F A C P, Altoona, Pa , spoke on "Schuller-Christian Disease"

The American Therapeutic Society held its 43rd Annual Meeting in Cleveland, Ohio, during June At this meeting Dr Harold S Davidson, F A C P, Atlantic City, N J, was elected President, Dr Francis D Murphy, F A C P, Milwaukee, Wis, and Dr Euclid M Smith, F A C P, Hot Springs National Park, Ark, Vice Presidents, Dr Oscar B. Hunter, F A C P, Washington, D C Secretary, Dr Daniel L Sexton, F A C P, St Louis, Mo, Treasurer, and Dr Francis M Pottenger, Jr (Associate), Monrovia Calif, Editor

Dr Jonathian C Meakins, F A C P , Montreal, Que , Regent and former President of the College, has been appointed Dean of the Faculty of Medicine of McGill University. Dr Meakins is also Professor of Medicine and Director of the Department at McGill University. Physician-in-Chief and Director of the University Clinic at the Royal Victoria Hospital.

Dr Lowell Ashton Elf (Associate), formerly Instructor in Clinical Medicine, and Research Associate in the Crocker Radiation Laboratory of the University of California, has accepted an appointment with Jefferson Medical College of Philadelphia, beginning with the September, 1941, term.

Dr William G Leaman, Jr , F A C P , Philadelphia, Pa , has been appointed Clinical Associate Professor of Medicine at the Woman's Medical College of Pennsylvania and Visiting Physician at the Philadelphia General Hospital.

Dr Samuel M Feinberg, F A C P , Chicago, Ill , has been elected to honorary membership in the Argentine Society for the Study of Allergy.

Dr William R Mathews, F A C P , Shreveport, La , has been elected President of the Louisiana Association of Pathologists.

The American Federation for Clinical Research was organized at Atlantic City, N J , May 5, 1941. Dr Maurice A Schnitzer (Associate), Toledo, Ohio, was elected President, and Dr Thomas M Durant, F A C P , Philadelphia, Pa , Secretary-Treasurer.

Dr Logan Clendening, F A C P , Kansas City, Mo , spoke on "Some Memorials of Medicine in America" at a recent meeting of the Hollywood (Calif) Academy of Medicine.

Dr Walter H Baer (Associate), Manteno, Ill , has been elected President of the Illinois Psychiatric Society.

Dr Philip F Barbour, F A C P , Louisville, Ky , was one of the guests of the Union County Medical Society who recently conducted a pediatric conference at Morganfield, Ky. Dr Barbour discussed "Chronic Heart Disease" and "Diarrhea and Dysentery."

Dr Maurice C Pincoffs, F A C P , Baltimore, Md , was elected one of the Vice Presidents of the Medical and Chirurgical Faculty of Maryland at its recent meeting in Baltimore.

Dr Walter Lincoln Palmer, F A C P , Chicago, Ill , spoke on "Diagnosis and Treatment of Gastric Disease" at the annual one-day clinic of the alumni of Wayne University College of Medicine.

Among the speakers at a conference on serology and syphilis control, held in Ann Arbor, Mich , sponsored by the American Association of Industrial Physicians and Surgeons, the U S Public Health Service, and the American Social Hygiene

Association, were Dr George H Gehrman, F A C P , Wilmington, Del , Dr Udo J Wile, F A C P , Ann Arbor, Mich , Dr Walter M Simpson, F A C P , Dayton, Ohio, Dr Otis L Anderson, F A C P , U S Public Health Service, and Dr Charles Walter Clarke, F A C P , Caldwell, N J

Dr John A McIntosh, F A C P , San Antonio, has been elected one of the Vice Presidents of the Texas Neurological Society

Dr Dolph L Curb, F A C P , Houston, has been elected one of the Vice Presidents of the Texas Society of Gastro-Enterologists and Proctologists

Dr Charles T Stone, F A C P , Galveston, has been elected President of the Texas Heart Association, Dr William B Adamson, F A C P , Abilene, Vice President, and Dr Victor E Schulze, F A C P , San Angelo, was reelected Secretary

Dr Carl J Wiggers, F A C P , Cleveland, Ohio, received the honorary degree of Doctor of Science from the University of Michigan at the Commencement, June 21, 1941

The Washington State Medical Association held its 52nd Annual Meeting in Seattle, August 24-27, 1941 Among the speakers at this meeting were

Dr Edwin G Bannick, F A C P , Seattle—"General Status of Chemotherapy",
Dr Lester J Palmer, F A C P , and Dr George D Capaccio (Associate),
Seattle—"Present Day Insulins"

Dr Andrew C Ivy, F A C P , has been elected President of the Chicago Society of Internal Medicine Dr Harold C Lueth, F A C P , Evanston, Ill , has been elected Vice President of the Society, and Dr Richard B Capps (Associate), Secretary-Treasurer

Dr David P Barr, F A C P , for a number of years Professor of Medicine at Washington University School of Medicine and Physician-in-Chief to the Barnes Hospital, St Louis, has been appointed Professor of Medicine and Physician in Chief to New York Hospital Dr Barr succeeds Dr Eugene F Du Bois, F A C P , who has been made Professor of Physiology and Head of the Department of Physiology and Biophysics

The 3rd biennial Rocky Mountain Medical Conference was held at Canyon Hotel, Yellowstone National Park, September 2-4, 1941 Among the speakers at this meeting were

Dr Clarence M Hyland, F A C P , Los Angeles, Calif—"Convalescent Human Serum Therapy, Serum and Plasma as Blood Substitutes",

Dr James G Carr, F A C P , Chicago, Ill—"Clinical Diagnosis of Coronary Occlusion" and "Cardiac Irregularities and Paroxysmal Tachycardia"

The Connecticut State Medical Society held its 17th Clinical Congress at New Haven, September 16-18, 1941 Among the guest speakers were.

Dr Irvine H Page (Associate), Indianapolis, Ind—"Hypertension",
 Dr Samuel A Levine, F A C P, Boston, Mass—"Modern Treatment of Congestive Heart Failure",
 Dr Burrill B Crohn, F A C P, New York, N Y—"Diagnosis and Treatment of Bleeding from the Stomach"

The Medical Society of the State of Pennsylvania will hold its 91st Annual Session in Pittsburgh, Pa, October 6-9, 1941. The meeting will consist of morning general assemblies, round table conferences, afternoon section programs on Medicine, Surgery, Eye, Ear, Nose and Throat Diseases, Dermatology, Urology, Obstetrics and Gynecology, Pediatrics, and Clinical Laboratory Medicine, and scientific and technical exhibits. All physicians, residents of Pennsylvania and of adjacent states who are members of, or are eligible to membership in, a county medical society, are cordially invited to attend this meeting. There is no registration fee.

Among the out-of-state guest speakers will be

Dr Charles A Waters, F A C P, Baltimore, Md—"Has Preoperative Irradiation a Place in the Treatment of Renal Tumors?",
 Dr Albert M Snell, F A C P, Rochester, Minn—"Changing Conceptions of Portal Cirrhosis",
 Dr Edward J Steglitz, F A C P, Garrett Park, Md—"Problems of the Aging",
 Dr Charles A Doan, F A C P, Columbus, Ohio—"The More Common Blood Dyscrasias—Their Diagnosis and Treatment"

The Omaha Mid-West Clinical Society will hold its 9th Annual Assembly in Omaha, Nebr, October 27-31, 1941. Among the members of the College who will present papers at this meeting are Dr W Osler Abbott (Associate), Philadelphia, Pa, Dr S Bernard Wortis, F A C P, New York, N Y, Dr Byrl R Kirklin, F A C P, Rochester, Minn, and Dr Albert M Snell, F A C P, Rochester, Minn.

Lt Commander Stanton Tice Allison, Medical Corps, U S N R (F A C P) has been appointed chief of medicine, U S Naval Hospital, Brooklyn, N Y.

1942 PROGRAM OF INTENSIVE POSTGRADUATE COURSES ARRANGED BY THE AMERICAN COLLEGE OF PHYSICIANS

The Advisory Committee on Postgraduate Courses, with the approval of the Committee on Educational Policy and the Executive Committee of the College, announces the following tentative program of postgraduate courses for the winter and spring of 1942. Some details are yet to be completed, but all the institutions mentioned have indicated a willingness to cooperate fully and many of the directors of courses are already outlining the courses and organizing their faculties.

This will be the fifth year of this activity by the College. The courses are organized especially for Fellows and Associates of the College, but where facilities are available, courses will be open to those with adequate preliminary training who are now preparing either to meet the requirements of membership in the College or certification by the American Board of Internal Medicine.

The courses are made available by the College to its members at minimum cost, because the College assumes full responsibility for promotion, advertising, printing and registration. The tuition will be \$20.00 for each week. All tuition fees are paid in bulk sum to the institution or director and faculty of each course. Registrations will not be accepted until later in the year when the formal Post-graduate Bulletin and registration form have been distributed.

The program of courses has again been expanded to meet the growing popularity of these courses. Some of the courses will be given during February and others, at more convenient centers, just preceding the Annual Session of the College at St. Paul, Minn. (April 20-24, 1942)

Tentative Schedule of Courses

A General Medicine

- 1 University of Minnesota Center for Continuation Study, Minneapolis
C. J. Watson, M.D., Professor of Medicine, *Director*
Two weeks, April 6-18, 1942 \$40.00
- 2 University of California Medical School and Stanford University School of Medicine, San Francisco
Directors to be announced
Two weeks, February 2-14, 1942 \$40.00

B Allergy

- 1 The Roosevelt Hospital, New York City
Robert A. Cooke, M.D., *Director*
Two weeks, February 2-14, 1942 \$40.00
- 2 Washington University School of Medicine and Barnes Hospital, St. Louis
Harry L. Alexander, M.D., Professor of Clinical Medicine, *Director*
Two weeks, April 6-18, 1942 \$40.00

C Cardiovascular Diseases

- 1 Peripheral Vascular Diseases
Mayo Foundation, University of Minnesota, and Mayo Clinic, Rochester
Edgar V. Allen, M.D., Associate Professor of Medicine, *Director*
Two weeks, April 6-18, 1942 \$40.00
- 2 Cardiovascular Disorders
Massachusetts General Hospital, Boston
Paul D. White, M.D., *Director*
Two weeks, February 2-14, 1942 \$40.00

D Gastro-Intestinal Diseases

- 1 University of Pennsylvania Graduate School of Medicine, Philadelphia
Henry L. Bockus, M.D., Professor of Gastro-enterology, *Director*
One week, February 2-7, 1942 \$20.00
- 2 University of Chicago, School of Medicine, Chicago
Walter Palmer, M.D., Associate Professor of Medicine, *Director*
Two weeks, April 6-18, 1942 \$40.00

E Arthritis and Rheumatism

- Mayo Foundation, University of Minnesota, and Mayo Clinic, Rochester
Philip S. Hench, M.D., Associate Professor of Medicine, *Director*
One week, April 13-18, 1942 \$20.00

Other courses, including one in General Medicine of two weeks' length during February in the East, and one in Tuberculosis of one week during April in the West, are under consideration, and announcements will be made later.

ANNALS OF INTERNAL MEDICINE

VOLUME 15

OCTOBER, 1941

NUMBER 4

MASS IMMUNIZATION AGAINST TYPHUS FEVER *

By R E DYER, Senior Surgeon, U S Public Health Service †

IN the control of typhus fever we are faced with a problem presented by a disease which is transmitted in nature by two arthropod vectors of different genera. The epidemiological picture, based as it is on the arthropod-host relationship and feeding habits of the vectors, is divided into two types. One of these epidemiologic types, to which we usually refer as endemic typhus, is determined by the life history of the rat flea (*Xenopsylla cheopis*) and the second, or epidemic type, by the life history of the body louse (*Pediculus corporis*).

The rat flea acquires its infection in nature by feeding upon typhus-infected rats. As a result, this flea-borne, endemic, or murine typhus occurs especially in persons exposed on rat-infested premises and does not become epidemic except under conditions of heavy rat and flea concentration. The flea does not transmit this infection from man to man. Endemic typhus is present over large sections of the southern states, and, recently, has invaded some of the more northern states of the middle west. The incidence, although increasing, is yet relatively low, approximately 3,000 cases being recognized annually in this country. It is theoretically possible that this flea-borne typhus may become epidemic in character through the agency of the body louse. That has apparently not occurred in this country, possibly because body lice are relatively rare in the sections where endemic typhus is most prevalent, and because other factors seemingly necessary for typhus epidemic formation, such as war, famine, and concentrated human misery are lacking. Dependent as it is on a reservoir of typhus in the rodent population, the control of the endemic form of the disease rests with the control of the rodent population and the use of a specific immunizing agent would be largely limited to protection of those exposed especially in food handling establishments, warehouses, and like establishments which are apt to maintain rat harbors.

* Read at the Boston meeting of the American College of Physicians, April 25, 1941

† National Institute of Health, Bethesda, Maryland

An entirely different problem confronts us in the control of the epidemic or louse-borne type of typhus. This form of the disease has its reservoir in man. With the presence of body lice and a few cases of typhus, epidemics of the typhus may occur. The seriousness of these epidemics is directly proportional to the misery of the population attacked. In a well-organized population, with little overcrowding, louse-borne typhus is readily controlled by delousing measures and even without such measures would probably not cause the development of a typical typhus epidemic with the cases and deaths numbered by the thousands or by the millions as in Russia in the years 1920-22. However, the factors which favor the development of large typhus epidemics are the same factors which disorganize civil governments—war, famine, and civil revolution. Under such conditions civil organization breaks down and the carrying out of effective delousing measures becomes impossible. For this reason efforts have been made for many years by various workers to develop a vaccine. With the present conditions in large sections of the world operating for the increase of human misery and wretchedness which are the companions of typhus epidemics this seems an opportune time to review what we know of typhus vaccines.

The search for a typhus vaccine has followed two general lines: one has been based on the use of living virus, and the second has sought for the production of a killed vaccine. The French investigators have almost uniformly attempted to utilize the living agent as a vaccine while others have directed their efforts to the second method.

LIVE VIRUS VACCINES

Attempts have been made by various workers to use the living agent as a vaccine. In the first attempts epidemic strains of virus were used as in Nicolle's experiments¹. In these he was able to produce an immunity in volunteers using blood serum from infected monkeys or the brains of infected guinea pigs as a source of virus. However, this did not prove a practicable method since the concentration of the virus varies with the animal and there is no feasible method of titrating that concentration prior to injection. The same difficulty was encountered by investigators who tried to prepare mixtures in which the virus was partially neutralized by convalescent serum. In vaccines of this sort there is always the danger of producing a typical, and possibly a severe, attack of the disease. As a result attempts along this line were largely dropped until the discovery of the milder endemic or murine type of the disease. Since this discovery two groups of French investigators, one headed by Laigret,^{2, 3, 4, 5} the second by Blanc,^{6, 7} have done a great deal of work with live vaccines made from murine typhus strains. There is little, if any, difference in the principles involved in the work of these two groups, the variations being in the technics used.

Laigret and his colleagues used a strain of endemic typhus and made preparations from the brains of typhus-infected guinea pigs. The etiologic

agent was found by them to retain its infectivity for more than three months if dried in egg yolk and stored at low temperatures. To modify the severity of the reaction they suspended this brain-egg yolk preparation in olive oil shortly before inoculating human beings. Recent work of Laigret and Durand has suggested that the infection in mice is somewhat more stable as regards virulence than the infection in guinea pigs and, further, that there is an increase in virulence for this species when passed by intracerebral inoculation. This suggests the possibility of the development of a fixed virus.

The second group attempting to utilize living material has employed first the tunica of guinea pigs infected with murine typhus and, more recently, the excreta of typhus-infected fleas. Blanc and his associates originally used a suspension of macerated guinea pig tunica taken shortly before the time of inoculation of subjects. To modify the severity of the infection they diluted the material 2,000 times and added sterile ox-bile to equal 5 per cent of the volume. The mixture was then allowed to stand for 15 minutes before use as a vaccine. One objection to this method was the difficulties encountered in preparing the vaccine shortly before use. This particular difficulty has been obviated by the more recent work of Blanc and Baltazard in which they have employed the excreta of typhus-infected fleas as a source of virus. They have found that when such excreta are dried the infection remains viable for approximately two years. Ox-bile is used as a medium for suspension just prior to inoculation, as was their method with the guinea pig tunica preparations.

Other investigators have attempted to produce mild typhus infections for the purpose of immunization by feeding infected material (Nicolle⁸) or by the instillation of such material on the conjunctivae (Sparrow⁹). In Nicolle's experiments he succeeded in producing mild but irregular infections in monkeys by feeding them the brains of infected guinea pigs. Sparrow used human volunteers and reported the production of a mild infection with subsequent immunity.

The laboratory experiments with the various modifications of live virus apparently justify the conclusion that an immunity can be established by this method. We can assume at least that living vaccines will produce a certain degree of immunity if infection with typhus follows the inoculation. The concentration of the infection in these vaccines is certainly so low that it can hardly be expected to produce an immunity without actual infection. The difficulties attendant upon these methods are inherent from the lack of a practical method of titrating the virulence of the vaccine or the resistance of the subject.

It is stated (Gaud¹⁰) in the reports on the vaccination of two million or more residents of North Africa that the reactions produced in natives are mild. Apparently the vaccination of Europeans is often followed by more severe reactions than usually seen in natives. This proved true in the only instance in which the use of live vaccine has been reported for the Western

hemisphere The reports on the protection afforded the natives of North Africa against subsequent attacks of typhus are difficult to analyze since apparently no unvaccinated control group was set up, nor is it clear that those giving history of a previous attack of typhus were excluded from the experiment

To summarize the work on live vaccines it may be stated that they probably produce an immunity commensurate with the severity of the reaction and that this immunity would be sufficient to aid materially in the control of a typhus epidemic The reactions reported make it inadvisable to use such vaccine for the protection of Europeans or Americans if some safer method can be found

KILLED VACCINES

Before the successful cultivation of rickettsiae in tissue cultures the only sources of infected material from which a killed vaccine might be made were infected animals and infected arthropods, at that time—lice The first attempts were made with infected animal tissues in which the infection was killed by heat or by some chemical It was found that such preparations, made from tissues of animals infected by intraperitoneal inoculation, produced no immunity, probably due to the low concentration of virus in the animal tissues Zinsser¹¹ succeeded in increasing the number of rickettsiae in rats by first injecting them with benzol and olive oil Later he used vitamin-deficient guinea pigs or rats which had received preliminary roentgen-ray treatment Rickettsiae were harvested from the peritoneal cavities of these animals and killed with formalin Suspensions of these killed rickettsiae were shown to produce immunity in guinea pigs and also in human volunteers (Varela¹²) The difficulties encountered in the production of rickettsiae by this method, although less than those encountered in the Weigl method (*infra*) did not give a great deal of encouragement in the problem of producing vaccine for mass immunization A further step in the use of animals as a culture medium for rickettsiae was made by Castaneda¹³ He was able to produce large numbers of rickettsiae by the intranasal inoculation of rats and mice with infectious material from a strain of endemic virus Such inoculations produced a rickettsial pneumonia in which the lungs of the animals showed great numbers of the organisms Castaneda found that formalinized suspensions of these rickettsiae would protect guinea pigs and human volunteers against infectious doses of the homologous strain Durand and associates^{14, 15} have shown that Castaneda's method is applicable to epidemic strains This method, though not without risk to the personnel of the manufacturing laboratory, is feasible for large-scale production of vaccine

A second method of vaccine production utilized the intestines of the body louse as a living culture medium for the production of rickettsiae Da Rocha-Lima,¹⁶ noting that the concentration of virus in infected lice was higher than in human blood, used carbolized suspensions of naturally infected

lice to protect guinea pigs. Since he relied on lice infected by feeding on cases of typhus, the possibilities of vaccine production by this method were very limited. However, two years later Weigl¹⁷ developed a technic for inoculating lice per rectum with suspensions of rickettsiae. Bierni¹⁸ used Weigl's technic for the inoculation of lice and made a carbolyzed suspension of the infected louse intestines. He found that such suspensions afforded protection to guinea pigs. The technic of this method was improved further and has been used for the production of vaccine for human inoculations on a surprisingly large scale. Briefly, the Weigl method of vaccine production requires the injection of lice per rectum with suspensions of rickettsiae. The lice are then fed on immune individuals to secure multiplication of the rickettsiae. This period of feeding is followed by dissection of the lice and the removal of the intestines. These intestines, triturated in carbolyzed salt solution, constitute the vaccine. Roughly, it requires the intestines of 100 lice for enough vaccine to vaccinate one person. Weigl's vaccine has been used probably as extensively as the supply permitted and has apparently given a good degree of immunity against the disease. One report by Weigl may be cited¹⁹ in which he states that of 2755 persons inoculated none developed typhus although all were later exposed. There are reports of cases where vaccinated individuals subsequently developed typhus, usually reported as mild, or modified, but on the whole it is the general opinion that Weigl's vaccine produces an immunity sufficient to control epidemics but probably neither an absolute nor a permanent immunity. When one considers the number of vaccinations necessary to immunize any large section of the population it becomes apparent that Weigl's method of preparation is too cumbersome to permit manufacture in sufficient quantities. However, enough of this vaccine probably could be produced to protect doctors, nurses, and orderlies engaged in the care of typhus cases during epidemics.

One other method has been developed for the cultivation of large numbers of rickettsiae in the production of vaccine. This method had its beginning in Nigg's²⁰ success in cultivating rickettsiae in tissue cultures. Kligler next cultivated a European typhus virus by using guinea pig tunica in normal saline and reported the protection of guinea pigs with a formalinized emulsion of these cultures. This was confirmed by Bengtson²² who used Maitland's medium as a base. Zinsser²³ improved on this method by using a specially prepared agar on which the infected animal tissue was spread. At first Zinsser used material from guinea pigs as a source of inoculum but later, after the successful work of Barykine²⁴ and of Cox²⁵ in cultivating large numbers of rickettsiae in the yolk sac of the developing chick embryo he used similar cultures as a source for his inoculum.

Liu,²⁶ using Zinsser's method, reported an increase in the agglutinins for *Proteus* OX₁₀ in inoculated individuals.

The Cox method of vaccine preparation is briefly as follows. Fertile eggs are incubated six to seven days, the inoculum is then injected into the yolk sac through a small hole in the air-sac end of the egg with a 1¼ inch

21-gauge needle The eggs are then incubated until death of the embryo which usually occurs in five to seven days The tissues are removed, washed in saline, pooled, and ground with alundum The mixture is made up to a 10 per cent suspension, of saline containing formalin Cox has shown that such a vaccine, made with an European strain of typhus, will effectively protect guinea pigs against the homologous strain

Tchang,²⁷ using the Cox method with a "Chinese" strain of typhus virus, confirmed Cox's results on the production of immunity in guinea pigs He stated further that 40 persons had been inoculated with this vaccine in Peking and that the final results would be reported later

Kurotchkin and Wyckoff²⁸ made a comparative study of the Zinsser and Cox methods of vaccine production and found that the Cox vaccine was at least as effective an immunizing agent as the Zinsser vaccine and that this method gave also a more satisfactory answer to the question of cost and ease of quantity production

SUMMARY

Aside from vaccines made from living infectious material there are three methods of typhus vaccine production available Weigl's louse intestine vaccine, Castaneda's mouse or rat lung vaccine, and Cox's yolk-sac vaccine Zinsser's final method is apparently a modification of the Cox technic, is somewhat more difficult to prepare, and apparently does not produce any better immunity in guinea pigs Weigl's vaccine, although it seems to produce a good degree of immunity, is too cumbersome for large scale production The two remaining vaccines, those of Castaneda and of Cox, can be produced in quantity and, from available results on animals, give promise of producing an immunity in man Experimentally, Castaneda's vaccine has been shown to protect man against subsequent inoculation with infectious material The final answer on both vaccines awaits their use under controlled conditions in the presence of a typhus epidemic Neither of these vaccines has been tried out adequately under such conditions although vaccine prepared by the Cox method is now on trial, in various countries where there is danger of epidemic typhus—Roumania, Hungary, Spain and China

REFERENCES

- 1 NICOLLE, C L'immunité et l'immunisation contre le typhus exanthématique Position et état actuel de la question, *Rev d'Immunol*, 1935, 1, 9-36
- 2 LAIGRET, J, and DURAND, R Technique de la desiccation et de l'enrobage du virus typhique murin, *Arch Inst Pasteur de Tunis*, 1936, 11, 82-88
- 3 LAIGRET, J, et al La vaccination contre le typhus exanthématique en Tunisie, *Bull Office Internat d'hyg publ*, 1938, 11, 308-316
- 4 LAIGRET, J, and DURAND, R Modification de l'activité pathogène de deux souches de virus typhiques murins entretenues par passages sur les souris blanches, *Compt rend Acad d sci*, 1939, 208, 673-675
- 5 LAIGRET, J, and DURAND, R La vaccination contre le typhus exanthématique Nouvelle technique de préparation du vaccin emploi des cerveaux de souris, *Bull Acad Med*, 1939, 11, 84-89 (Abstract), *Bull Soc Path Exot*, 1939, 11, 735-751

- 6 BLANC, G, and BALTAZARD, M Recherches sur la durée de l'immunité conférée à l'homme par l'infection fébrile ou inapparente de typhus murin, *Compt rend Acad d sci*, 1939, cciv, 419-420
- 7 BLANC, G, and BALTAZARD, M Bull Acad Med, 1937, cxviii, 116 Vaccination contre le typhus exanthématique par virus sec de typhus murin provenant de puces infectées, *Compt rend Acad d sci*, 1938, ccvii, 547-548 Recherches sur la durée de l'immunité conférée à l'homme par l'infection fébrile ou inapparente de typhus murin, *Ibid*, 1939, cciv, 419-420
- 8 NICOLL, C, et al *Compt rend Acad d sci*, 1933, cxcvii, 1709
- 9 SPARROW, H, and MARFSCHAL, P Essais d'immunisation de l'homme par voie oculaire avec les rickettsies du virus murin I de Tunis, Bull Acad Med, 1938, cxix, 140-145
- 10 GAUD, M La vaccination contre le typhus par la méthode de G Blanc au cours de l'épidémie de 1937 au Maroc, Bull Office Internat d'hyg publ, 1938, xxx, 298-307 and 2751-2758
- 11 ZINSSER, H, and RUIZ CASTANEDA, M Further experiments in typhus fever, infection with washed Mexican Rickettsiae and immunity to European typhus, Jr Exper Med, 1930, lii, 865-871 Studies on typhus fever, active immunization against typhus fever with formalinized virus, *Ibid*, 1931, liii, 325-331
- ZINSSER, H, and SEASTONE, C V, JR Studies on typhus fever, reduction of resistance by diet deficiency, *Ibid*, 1931, liii, 333-338 Studies on typhus fever, active immunization against Mexican typhus fever with dead virus, *Ibid*, 1931, liii, 493-497 Studies on typhus fever, on serum reactions of Mexican and European typhus Rickettsia, *Ibid*, 1932, lvi, 455-567 Studies on typhus fever, further experiments on active immunization against typhus fever with killed Rickettsia, *Ibid*, 1933, lvii, 381-390
- 12 VARELA, G, et al Active immunization against Tunisian typhus fever with Mexican typhus vaccine, Proc Soc Exper Biol and Med, 1932, xxx, 206-209
- 13 CASTANEDA, M R Experimental pneumonia produced by typhus Rickettsiae, Am Jr Path, 1939, xv, 467-476
- 14 DURAND, P, and SPARROW, H Inoculation pulmonaire des virus typhiques et boutonneux, *Compt rend Acad d sci*, 1940, ccx, 420-422
- 15 DURAND, P, and GIROUD, P Essais de vaccination contre le typhus historique au moyen de rickettsias tuées par le formol (souches pulmonaires), *Compt rend Acad d sci*, 1940, ccx, 493-496
- 16 DA ROCHA LIMA, H Schutzimpfungsversuche gegen Fleckfieber, Munchen med Wchnschr, 1918, lxxv, 1454-1456
- 17 WEIGL, R Ueber aktive Fleckfieberimmunität, Med Klin, 1924, xx, 1046-1049 Untersuchungen und Experimente an Fleckfieberläusen Die Technik der Rickettsia-Forschung, Beitr z Klin d Infektionskr Wurzb, 1919-1920, viii, 353-376
- 18 BREINL, F Studies on typhus virus in the louse, Jr Infect Dis, 1924, xxxiv, 1-12
- 19 WEIGL, R Arch Inst Past de Tunis, 1933, xxii, 315
- 20 NIGG, C, and LANDSTEINER, K Proc Soc Exper Biol and Med, 1930, xxviii, 3 Note on cultivation of typhus fever Rickettsia, *Ibid*, 1932, xxix, 1291
- 21 KLIGLER, I J, et al Proc Soc Exper Biol and Med, 1933, xxxi, 349
- KLIGLER, I J, and LEVINE, S Immunization of monkeys and humans with formalized tissue cultures of Typhus rickettsia, Trans Roy Soc Trop Med and Hyg, 1938, xxxii, 93-98
- 22 BENGTON, I A Cultivation of rickettsiae of endemic (murine) and epidemic (European) typhus fever in vitro, Pub Health Rep, 1937, lii, 1336-1340
- 23 ZINSSER, H, et al Further studies of agar-slant tissue cultures of typhus Rickettsiae, Proc Soc Exper Biol and Med, 1938, xxviii, 285-288 Nouvelles méthodes de culture de Rickettsiae du typhus a propos de la production de vaccins, *Compt rend Soc d biol*, 1938, ccxvii, 229-232 Study of Rickettsiae grown on agar tissue cultures, Jr Exper Med, 1939, lxi, 179-190

- 24 BARYKINE, W, et al Nouvelle methode de culture du virus du typhus exanthématique, Bull Office Internat d'hyg publ, 1938, xxx, 326-331
- 25 COX, H R Use of yolk sac of developing chick embryo as medium for growing *Rickettsiae* of Rocky Mountain spotted fever and typhus groups, Pub Health Rep, 1938, liii, 2241-2247
- 26 LIU, P Y, and ZIA, S H Weil Felix reaction following typhus vaccination, Chinese Med Jr, Supp 3, 1940, 487-494
- 27 TCHANG, J, and MATHEWS, G B Anti-typhus vaccine prepared from *Rickettsia prowazeki* cultivated in yolk sac of developing chick embryo, Chinese Med Jr, 1940, lviii, 440-445
- 28 KUROCHKIN, T J, and WYCKOFF, R W G Immunizing value of rickettsial vaccines, Proc Soc Exper Biol and Med, 1941, xlv, 223-228

CEREBRAL EMBOLISM IN MITRAL STENOSIS¹

By ALFRED W. HARRIS, M.D., *Dallas, Texas* and SAMUEL A. LEVINE, M.D.,
F.A.C.P., *Boston, Massachusetts*

THERE has been little investigation of the exact type of cardiac patient who is most likely to develop cerebral embolism. Likewise little attention has been paid to the immediate mortality and subsequent developments of such a cerebral complication. The purpose of this study is to analyze the data available in a group of cases of mitral stenosis that had clinical evidence of cerebral embolism. It is not the purpose to investigate cerebral embolism that occurs as a part of bacterial endocarditis nor is it our purpose to study the dislodgement of uninfected mural thrombi such as may appear following coronary thrombosis with myocardial infarction.¹ The latter problem has been studied recently^{2,3} and it was emphasized that sudden hemiplegia or so-called apoplectic strokes occurring in patients without hypertension are often misdiagnosed as instances of cerebral hemorrhage when in fact they are the result of embolism from a left ventricular mural thrombus after myocardial infarction.

In this present investigation cases were included only if there was clear cut evidence of mitral stenosis and clinical reason to believe that a rupture of a cerebral vessel had not occurred. It was not always possible to be certain of this latter point but in young or middle aged patients with little or no elevation of blood pressure we have assumed that a sudden cerebral accident was due to embolism. The validity of this assumption was enhanced by the fact that many of the cases showed evidence of embolism in other parts of the body and that about 25 per cent of the fatal cases were confirmed by postmortem examination. As evidence of gross cerebral accident only those cases were included in which sudden obvious paralysis occurred of one or more limbs, or of the face. In this way 48 cases were accumulated from the records of the Peter Bent Brigham Hospital and 24 cases from the private practice of one of us.

This survey was prompted by the clinical observation that many cases of mitral stenosis have a sudden cerebral embolism while otherwise in a fair state of cardiac compensation. It seemed that the typical case was one in which paralysis occurred suddenly at a time when there was no complaint of dyspnea and the patient was able to lie flat in bed, and had been ambulatory. In fact, it also seemed that after gross congestive failure had developed in patients with advanced mitral stenosis, although they might be observed over the course of years, cerebral embolism or hemiplegia was uncommon. It is well known that there are other antagonisms in clinical medicine in which the

* Received for publication June 29, 1940.

From the Medical Clinic of The Peter Bent Brigham Hospital and the Department of Medicine, Harvard Medical School.

presence of one type of condition makes it unlikely that another will develop⁴ An example of this is the rarity of angina pectoris in the presence of persistent auricular fibrillation^{5,6} or the infrequency of the development of subacute bacterial endocarditis *after* congestive failure has taken place^{6,7}

Of the 72 cases of mitral stenosis and cerebral embolism in this study, there were 26 males and 46 females This is a slightly lower predominance of the female sex than occurs with mitral stenosis in general⁸ The average age of the entire group was 42.7 years, the range being from 18 to 65 years Eighteen of the total number had hypertension and 54 did not The average level of the hypertensives was 171 mm of Hg systolic and 97 diastolic, the range being 155/75 to 230/130 Auricular fibrillation was present in 55 cases or 76.4 per cent of the series. Of these only three were transient fibrillators, in the others the arrhythmia was permanent Although the exact time of onset of auricular fibrillation preceding the cerebral episode could not be ascertained in all cases, some data bearing on the point were available Of the 55 cases of mitral stenosis and auricular fibrillation, in 26 instances persistent fibrillation was known to be present for varying times before the development of the embolism Obviously the arrhythmia may well have been present for some time before the first observation The duration of the observed fibrillation ranged from three days to nine years, with an average of 22 months There were four instances in which it was known that the irregularity had been present no longer than 28, 14, 14, and three days We have the impression that the cerebral accident is apt to occur during the early weeks or months after the onset of persistent auricular fibrillation In a small number of instances, five, where the fibrillating state reverted to a normal rhythm either spontaneously or following quinidine therapy, embolism took place within a few hours or a day or two after regularization of the beat had taken place⁹

It is noteworthy that in 17 instances (23.6 per cent) the rhythm was regular at the time the cerebral accident occurred and as far as could be ascertained fibrillation of the auricles had not taken place in the past As would be expected the average age of the "regular" group was 3.9 years less than that of the "fibrillators" For some unexplained reason there was only one male among the 17 regular cases

*When such a close relationship exists between a reversion to normal rhythm and development of embolism, it seems difficult to assume that the two events are coincidental^{9,10,11,12,13} It has been claimed¹⁰ that embolism occurs as readily in fibrillating hearts on digitalis as on quinidine therapy This conclusion not only seems untrue but the statistical evidence offered to support it contains an obvious arithmetical error The fact that the same number of emboli occur in a consecutive group of patients with auricular fibrillation on quinidine therapy as in a control group on digitalis therapy cannot be interpreted in the sense that the two drugs are equally blameworthy The average administration of digitalis in the control group continued over one or two years, whereas the quinidine was given only for several days Expressed in other words, during 50,000 days of digitalis administration, two emboli may have occurred, while during but 500 days' use of quinidine two emboli also occurred There can be no doubt that if a patient is fibrillating, is given quinidine, and within two or three days the heart rhythm becomes regular and a hemiplegia develops, the drug is the cause of the disaster It is not inferred that embolism cannot occur in long-standing cases of fibrillation In fact there was one instance in the group herein reported in which embolism took place nine years after the known onset of this arrhythmia

An attempt was made to learn something about the progress of the paralysis that occurred in these cases. Unfortunately the data available did not include sufficient details to enable one to draw accurate estimates. It did seem fairly clear, however, that when improvement occurred, most of it was manifest within one month. In the recovered cases available for study, it was found that approximately one-third of the group with focal motor palsies demonstrated slight recovery of function in one year, whereas the remaining two-thirds showed no change. Despite the poor motor recovery, relatively few patients were bedridden after the embolism. In contrast to the poor prognosis for recovery of function in those with motor palsies of the extremities or face, clearing of speech disturbances occurred in practically all the patients who survived the embolism.

Cases in this study were also analyzed from the point of view of the presence or absence of congestive heart failure at the time of the cerebral embolism. We used as evidence of heart failure the presence of râles or fluid in the chest, engorged liver or peripheral pitting edema. Simple dyspnea without objective signs of congestion was not accepted as evidence of failure for purposes of this study. Although this is an artificial division it enabled us to compare those cases that were ambulatory and in a fair degree of cardiac compensation with those whose disease was more advanced. In this sense there were 49 without and 23 with heart failure. It is obvious that there is a time factor in the development of cerebral embolism from a left auricular mural thrombus and that it may be looked upon as an accident of heart disease. It is also clear that patients have mitral stenosis a much longer time without heart failure than with failure. If auricular thrombi develop early in the progress of rheumatic disease there would naturally be a longer opportunity for embolism to develop during the compensated than during the decompensated state. The difficulty is that the exact time that mural thrombosis develops in the course of mitral stenosis is not known. There is no method of predicting its presence except when embolic manifestations result. The large number of cases with a regular rhythm emphasizes the fact that auricular mural thrombosis does not require auricular fibrillation for its development in the presence of mitral stenosis. In fact one wonders whether auricular fibrillation has much additional importance in influencing thrombus formation. However, it is quite likely that dilatation of the auricles and diminished motion of the walls are factors. It is possible also that active carditis with injury to the endothelial lining may play a rôle in the formation of these clots.

An analysis was made of the effect of the presence of hypertension, and of the regularity or irregularity of the cardiac mechanism, and of heart failure on the subsequent course of events following cerebral embolism. In the entire series of 72 cases, there were 24 deaths occurring within a few days or a few weeks following the accident. This means that there is a 33 per cent immediate mortality in the average case of mitral stenosis that has cerebral embolism. The average time of death after the embolism was 4.3

days In these cases it seemed fairly clear that embolic phenomena were the direct precipitating causes of the fatality Fifteen additional cases died at varying times from one month to seven years following the accident, the average duration of survival in this group being 13.2 months This indicates that after surviving the initial insult of a cerebral embolus these cases do not live on the average much longer than one year

Among the 18 hypertensive cases, there were six immediate fatalities and four patients died subsequently, with an average period of 19.7 months of survival In the 54 non-hypertensives, there were 18 immediate fatalities, and the average survival period of the 11 known to have died subsequently was 10.6 months Thus it is clear that the pressure level has no influence on the immediate mortality in these cases The greater survival period among the hypertensives is in accord with a previous study in which it was found that hypertension acts beneficially in cases of mitral stenosis⁷ The average age at the time of embolism in the hypertensive group was 47.5 years, while that in the non-hypertensives was 41.0 years Heart failure was somewhat more frequent in the hypertensives than in those with normal pressure, i.e., nine out of 18 in contrast to 14 out of 54 Likewise auricular fibrillation was more common in the former group, i.e., 16 out of 18 in contrast to 39 out of 54 It seems therefore that patients with mitral stenosis and cerebral embolism who have hypertension are apt to be older, to have auricular fibrillation, to have congestive failure, and are likely to survive for a longer period than those not having hypertension

A similar analysis was made of the rôle that auricular fibrillation might play in the progress of these cases Of the entire 72 patients, 55 had auricular fibrillation and 17 had regular rhythm Among the former there were 31 females and 24 males, whereas among the latter there were 16 females and only one male The average age of the fibrillators was 43.5 years and of the non-fibrillators 39.6 years There were 17 immediate fatalities among the former, and in the 14 of those dying subsequently the average survival period was 10.7 months In the non-fibrillators, there were seven immediate fatalities and the only one known to have died subsequently lived four years There was a greater incidence of hypertension among the fibrillators with mitral stenosis than in those with regular rhythm, there being 16 out of 55 in contrast to two out of 17 Similarly congestive failure was more common with (19 cases) than without auricular fibrillation (4 cases) It follows from the above survey that cases of mitral stenosis and cerebral embolism that have a regular rhythm are overwhelmingly of the female sex, that the fibrillators are older, have hypertension and congestive failure more frequently, but that the danger of an immediate fatality is not particularly influenced by the rhythm of the heart

The last point that was investigated was the rôle that congestive heart failure might be playing in these cases In the entire series of 72 cases, 23 had congestive failure and 49 had no failure The average age of the two groups was 43.1 years and 42.3 years respectively There was a much

greater immediate mortality among those with heart failure, i.e., 12 out of 23 cases as compared to 12 out of 49 cases without failure. The survival period of the six cases in the former group averaged 12 months and of the nine cases in the latter group averaged 14 months. As noted above hypertension was present more frequently in those with failure than in those who were compensated. It is of some interest that in all four instances where the rhythm was regular and congestive failure was present, "immediate mortalities" occurred, whereas in 13 regular cases without failure only four died. The obvious inference from the above data is that the presence of heart failure makes the immediate outlook more grave when cerebral embolism occurs in cases of mitral stenosis, especially when the rhythm is regular.

DISCUSSION

Sterile peripheral emboli in cases of mitral stenosis occur as a result of dislodgement of bits of thrombi that are present in the left auricular wall. There is no known method of detecting the existence of mural thrombi until peripheral embolism takes place. Furthermore, there is no definite information that would enable us to estimate when mural thrombosis occurs on the auricular walls and therefore how soon after its formation embolism is most likely to result.

The similar problem concerning mural thrombosis in the ventricular cavity is much more clearly understood. Here the main cause is coronary thrombosis and ventricular infarction, the onset of which can be clearly defined. It is known that in the great majority of instances embolism from a ventricular thrombus takes place from a few days to a few weeks after the formation of the thrombus and only rarely months or years later. One cannot draw a close analogy between the possibilities that obtain when thrombi are present in the ventricles and in the auricles. In the former case the thrombi are apt to be very large and the ventricular contractions and movements very vigorous. In the auricles the thrombi are quite small and the contractions are comparatively weak. In fact there are crevices in the auricular appendages where the blood flow must be very sluggish and when auricular fibrillation is present there must be practically no contractions of the auricular wall. Furthermore, the rate of blood flow is different in the two chambers. Slowing of the blood stream is more conducive to the formation of clots whereas acceleration of the stream would tend to dislodge them. For these reasons the auricles, where the current is slow, should be the favorite site for the formation of thrombi. However, once such thrombi are present in the auricles, it is likely that they may remain silent a long time. Just the reverse set of circumstances exist in the ventricles.

It is clear from the above that the factors for the formation and dislodgement of thrombi in the auricles are numerous and difficult to analyze. The effect of auricular fibrillation, for instance, is open to some speculation. It is generally assumed that this arrhythmia enhances the likelihood of

thrombosis and embolism The proof of this assumption is questionable From this study it is evident that the average age of the cases that had auricular fibrillation and cerebral embolism was 39 years greater than those with regular rhythm There was, therefore, a much longer period of time during which embolism could take place among the irregular than the regular cases One might infer that it was not because of this arrhythmia but rather because of the increasing age and the longer period of time, that so many of the cases had auricular fibrillation Furthermore, the large number of instances of embolism with regular rhythm indicates that thrombi can readily form in the auricles without fibrillation, and possibly even in those cases with fibrillation the thrombi may have formed earlier when the auricles were contracting normally

Another unknown factor in the formation of auricular thrombi is the rôle of acute rheumatic carditis with the possible involvement of the endocardium Because of the difficulty of detecting the presence or development of the thrombus until embolism results, it is difficult to ascertain the part played by infection and inflammation in this problem Only when more is known about the mechanism of auricular thrombosis will it be possible to attempt methods of prevention such as the recent introduction of the use of heparin¹⁴ might afford

SUMMARY

Seventy-two cases of mitral stenosis in which cerebral embolism occurred were studied

There were 26 males and 46 females The average age was 42.7 years

There were 24 "immediate fatalities" among the entire 72 cases, i.e., 33 per cent mortality The average period of survival of the 15 cases that died subsequently was 13.2 months

Hypertension was present in 18 of the 72 cases Hypertension had no effect on the "immediate mortality" but the survival period of those who recovered was distinctly longer (19.7 months) The average age of the hypertensives was 47.5 years and of the non-hypertensives 41.0 years Heart failure and auricular fibrillation were more common in the hypertensive group

Auricular fibrillation was present in 55 cases and regular rhythm in 17 cases Among the latter there was only one male The average duration of auricular fibrillation before embolism was 22 months In five instances ~~cerebral embolism occurred a few hours or a day or two after reversion to normal rhythm~~ The average age of the fibrillators was 43.5 years and of those with regular rhythm 39.6 years The "immediate mortality" and the survival period of those recovering from embolism were not influenced materially by the presence of auricular fibrillation, despite the fact that hypertension and congestive failure were more common in this group

There were 23 with and 49 without congestive heart failure The former had a much greater "immediate mortality" (53 per cent as com-

pared to 24 per cent) In all four cases of congestive failure with regular rhythm "immediate fatalities" occurred, while among 13 regular cases without failure, only four died

The prognosis for recovery of motor function after embolism was poor Speech disturbance, however, cleared in practically all cases

It seems that cerebral embolism is more likely to occur in cases of mitral stenosis that have very little objective evidence of congestive heart failure and is less apt to develop in those who are bedridden with advanced failure

Cerebral embolism occurs more frequently in compensated than in decompensated cases of mitral stenosis because the former state lasts longer than the latter

BIBLIOGRAPHY

- 1 LEVINE, S A Coronary thrombosis its various clinical features, 1929, Williams and Wilkins, Baltimore
- 2 DOZZI, D L Cerebral embolism as a complication of coronary thrombosis, *Am Jr Med Sci*, 1937, cxiv, 824
- 3 DOZZI, D L Unsuspected coronary thrombosis in patients with hemiplegia—a clinical study, *ANN INT MED*, 1939, xii, 1991
- 4 LEVINE, S A The destructive or elimination method of differential diagnosis a neglected aspect of medical teaching, *Medical Papers Dedicated to Dr Henry A Christian*, 1936, Waverly Press Inc, Baltimore
- 5 ROTHSCHILD, H A, SACKS, B, and LIBMAN, E The disturbances of the cardiac mechanism in subacute bacterial endocarditis and rheumatic fever, *Am Heart Jr*, 1927, ii, 356
- 6 LIBMAN, E The clinical features of subacute streptococcus (and influenzal) endocarditis in the bacterial stage, *Med Clin North Am*, 1918, ii, 117
- 7 FULTON, M N, and LEVINE, S A Subacute bacterial endocarditis with special reference to the valvular lesions and previous history, *Am Jr Med Sci*, 1932, clxxxiii, 60
- 8 LEVINE, S A, and FULTON, M N The relation of hypertension to mitral stenosis, *Am Jr Med Sci*, 1928, clxxxvi, 465
- 9 LEVY, R L The clinical toxicology of quinidine, *Jr Am Med Assoc*, 1922, lxxviii, 1919
- 10 VIKO, L E, MARVIN, H M, and WHITE, P D A clinical report on quinidine sulfate, *Arch Int Med*, 1923, xxxi, 345
- 11 PARKINSON, J, and CAMPBELL, M Quinidine treatment of auricular fibrillation, *Quart Jr Med*, 1929, xxi, 281
- 12 COOKSON, H The etiology and prognosis of auricular fibrillation, *Quart Jr Med*, 1930, xxiii, 309
- 13 SOKOLOW, M Quinidine in the treatment of benign auricular fibrillation with repeated emboli, *Am Heart Jr*, 1939, xviii, 494
- 14 BEST, C H Heparin and thrombosis, *British Med Jr*, 1938, ii, 977

PULMONARY INFARCTION IN HEART DISEASE¹

By LAURENCE E. HINES, M.D., F.A.C.P., and JORDAN T. HUNT, M.D.,
Chicago, Illinois

THE pathological changes of pulmonary infarction were known to Laennec, but he failed to recognize the relationship between embolism and infarction and called the condition "pulmonary apoplexy." Later, in 1856, Virchow pointed out the rôle of the embolus as the cause of lung infarcts. Over a period of many years numerous clinical, pathological, and experimental studies have established an accepted anatomical and clinical picture for pulmonary infarction. The typical pathological appearance of the lesion cannot be disputed. The necessary rôle of impaired pulmonary circulation in the development of the disease is also well established. The well known clinical syndrome seems sufficiently clear and generally is adequate to make the diagnosis of moderate-sized lesions which have been induced by emboli from surgical phlebitis. Observations at the necropsy table, however, have shown that patients with non-surgical diseases, like heart disease, frequently have extensive infarction of the lung that was not discovered during life. This fact stimulated the present survey of necropsy and clinical records from the Department of Pathology of Northwestern University, made available through the courtesy of Dr. James P. Simonds. The material was particularly well suited to a study of this kind because the records were compiled from four hospitals which represented such types as the large charity hospital, the private teaching hospital and one not affiliated with a university.

RESULTS

The survey covering 1311 necropsies performed in a six-year period revealed 101 cases with gross pulmonary infarction. The incidence (7.7 per cent) is similar to that reported by others. An extensive review by Hosai¹ revealed an incidence which varied from 0.65 per cent to 14.5 per cent.

Heart disease, the principal cause of death in 234 cases, was accompanied by gross pulmonary infarction 81 times (35 per cent), and yet a clinical diagnosis of pulmonary infarction was made only twice. This striking diagnostic failure prompted an analysis of the clinical symptoms and signs presented by these patients. As controls the patients with heart disease having no infarction were similarly analyzed. The results, compared in the tables, at once explain the high incidence of diagnostic failures. Symptoms thought of as characteristic of pulmonary infarction can also be explained as symptoms of heart failure. Patients presenting symptoms of hemoptysis, pleural pain, cough, dyspnea, cyanosis, fever, percussion dull-

* Received for publication June 25, 1940.

From the Department of Medicine, Northwestern University, Chicago, Illinois.

ness of pulmonary râles have received a diagnosis of heart failure rather than pulmonary infarct

An analysis of symptoms and signs of both groups reveals only minor differences, with the exception of hemoptysis which occurs in 35 per cent of

TABLE I
Autopsy Incidence of Pulmonary Infarction
(1931 to 1939)

Number of autopsies reviewed	1311
Patients dying of heart disease	234
Number of patients with pulmonary infarction	101
Cause of infarction Heart disease	81
Non cardiac	20
Clinical diagnosis of infarction (heart cases)	2

TABLE II
Necropsy Incidence of Pulmonary Infarction in Etiological Types of Heart Disease

	Number of Cases	Incidence of Infarcts	Incidence Per Cent
Hypertensive or arteriosclerosis*	161	48	30
Rheumatic type	33	12	36
Syphilitic	15	5	33
Bacterial	16	10	62
Congenital	1	0	0
Combined syphilis and arteriosclerosis	77	5	71
Combined rheumatic and arteriosclerosis	1	1	100
Total cases	234	81	34

* 19 of this group had coronary thrombosis

TABLE III
Comparative Frequency of Symptoms in Patients Dying of Heart Disease
With Pulmonary Infarction With No Pulmonary Infarction

	Total Cases	With Symptoms	% Incidence of Symptom	Total Cases	With Symptoms	% Incidence of Symptom
Hemoptysis	81	29	35%	161	12	8%
Pleural pain	81	13	16	161	14	9
Precordial pain	81	37	46	161	65	42
Cough	81	33	41	161	84	54
Shock or sudden death	81	10	12	161	30	19
Dyspnea	81	78	96	161	145	95
Asthmatic attacks	81	6	7	161	9	6

the patients who had infarction, whereas it occurred in only 8 per cent of the others. Studies of the quantity of blood expectorated might reveal even greater differences, but such information was not available. Observations on a small number of patients of the series point to persistent recurrent hemoptysis as a distinctive feature of the disease. A comparison of the incidence of pain, cough, dyspnea, symptoms of shock, cyanosis, fever, signs

of consolidation, signs of heart failure, and auricular fibrillation reveals no significant variation in the two groups. Table 2 shows the incidence of pulmonary infarction in the various etiologic types of heart disease. Although a higher incidence is present in bacterial endocarditis there is no essential difference in the rheumatic, vascular or syphilitic groups.

TABLE IV
Comparative Frequency of Physical Findings with Pulmonary Infarction

	Total Cases	With Finding	% Incidence of Finding	Total Cases	With Finding	% Incidence of Finding
Cyanosis	81	48	62	161	80	50
Fever	81	39*	48	161	52†	33
Signs of pulmonary consolidation	81	21	25	161	30	19
Signs of congestive heart failure	81	71	87	161	154	94
Auricular fibrillation	81	29	36	161	53	35

* 8 of this group had pneumonia

† 29 of this group had pneumonia

No accurate data on friction rub

TABLE V
Location of Infarct

Single Lobe Involvement	(43%)	Multiple Lobe Involvement	(57%)
	%		%
Right lower	23	Right upper	21
Right upper	2	Right lower	50
Right middle	1	Right middle	17
Left lower	15	Left upper	22
Left upper	2	Left lower	46

COMMENT

The infrequency of a clinical diagnosis of pulmonary infarction in this series is striking. Texts and articles dealing with this subject present the following clinical picture: Emboli large enough to occlude the pulmonary artery or main branches cause a symptom complex characterized by hemoptysis, marked dyspnea, cyanosis, substernal oppression and peripheral circulatory collapse (weak pulse, profuse sweating, ashen pallor, lowered blood pressure). This picture is mistaken sometimes for coronary thrombosis, but generally is sufficiently distinctive, even if heart disease is present, to lead to a correct diagnosis. Moderate sized emboli which occlude secondary and tertiary radicles of the pulmonary artery produce hemorrhagic infarcts and a syndrome characterized by sharp pleuritic pain in the lower chest, dyspnea, hemoptysis, mental anxiety, mild degree of shock, increase in pulse rate, fever, signs of pulmonary consolidation, râles, and a friction rub. Although this picture is typical of postoperative emboli, it is inadequate for diagnosis of moderate sized emboli in patients with heart failure. The discrepancy in clinical manifestations of the same process, when it occurs in

different diseases, can be explained by differences in associated pathological changes in the lung. Passive hyperemia, pulmonary edema, brown induration, pulmonary fibrosis, pleural effusion or emphysema may coexist. In every subject of this series one or more additional disease processes were associated with infarction. Frequently a single subject showed passive hyperemia, emphysema, bronchopneumonia and pleural effusion. Any of the disease processes may inhibit symptoms which the embolus in a normal lung is capable of producing. In particular the shock and pleuritic pain might well be diminished through damage to the nerve receptors by long standing passive congestion.

The other signs, such as dullness, cyanosis, friction rub or fever, if present, might be interpreted as a sign of some phase of heart failure.

It is, therefore, apparent that this important disease process, frequently causing consolidation in one or all lobes of the lung in patients with heart disease and capable of precipitating heart failure or delaying recovery, has no characteristic clinical syndrome in the presence of heart disease. Symptoms and signs are not reliable aids because they can be produced by other manifestations of the decompensated heart. As an aid in this diagnostic dilemma the following suggestions are made. In the management of heart disease the high incidence of this complication should be kept in mind, infarction of the lung should be considered if the patient has persistent or recurrent hemoptysis, persistent deep cyanosis, unexplained jaundice, unexplained fever or sudden onset of heart failure not explained by overexertion or infection. Finally, critical analysis of the roentgen-ray films of proved cases may lead to the establishment of typical roentgen-ray findings for this condition.

REFERENCE

- 1 HOSAI, KIYOSHI. Pulmonary embolism and infarction, *Ann Surg*, 1932, xcv, 67

THE CHEMISTRY OF VITAMIN K¹

By LOUIS F FIESER, PH D, *Cambridge, Massachusetts*

IN the following paper such aspects of the chemistry of vitamin K are surveyed as have a direct bearing on the present and future status of the use of this vitamin factor in practical therapy. The vitamin has proved very efficacious in the limited but important field of the treatment of hypoprothrombinemia associated chiefly with obstructions of the biliary tract and with the bleeding tendency of the newborn. The possibility of the uncovering of other clinical applications should not be overlooked.

Following Dam's discovery of the existence of a dietary antihemorrhagic factor in 1929,¹ a brief period of a few months in 1939 saw the isolation of pure vitamin K₁ from alfalfa,^{2,3} the elucidation of the chemical formula of the substance^{4,5} and its preparation by synthesis^{6,7}. Too little time has as yet elapsed for the general recognition that certain of the conjectures tentatively advanced in the early stages of the work have now been discarded, and that some of the early reports concerning the antihemorrhagic activity of synthetic compounds were invalidated by imperfections in the technic of the bio-assay. The situation has been confusing to the extent that even clinicians interested in vitamin K therapy have been among those to fall prey to some of the current misconceptions. One is that the family of K-vitamins includes a whole host of individual substances. Actually the known list of natural antihemorrhagic factors includes only vitamin K₁, from alfalfa, and vitamin K₂, from putrefied fish meal. Vitamin K₁ is 2-methyl-3-phytyl-1,4-naphthoquinone, and vitamin K₂ probably is 2-methyl-3-difarnesyl-1,4-naphthoquinone.⁸ The two substances are closely related in chemical structure, for they have the identical quinone nucleus and each possesses a long side-chain made up of the same, branched, five-carbon units (figure 1)

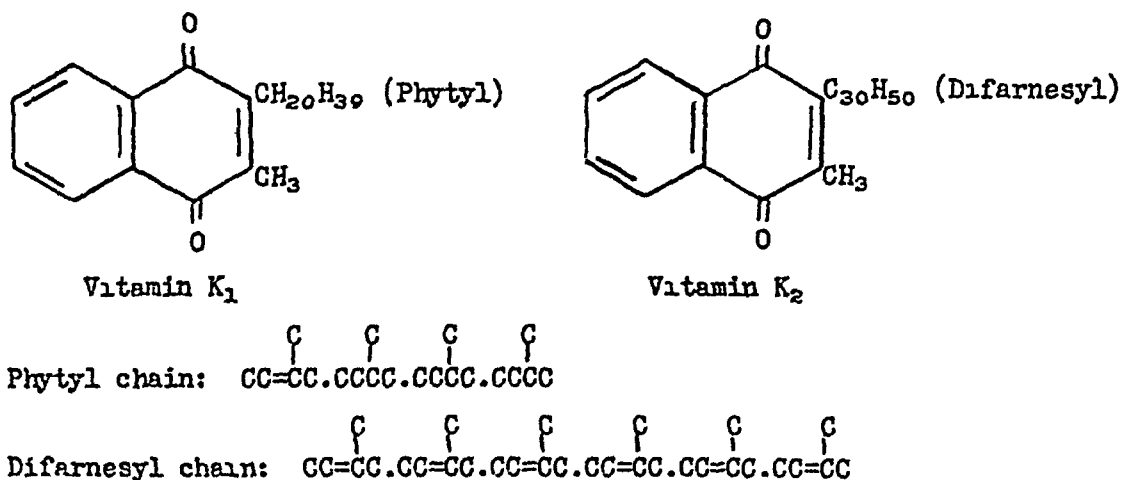


FIG 1 Structures of the vitamins

* Read at the Boston meeting of the American College of Physicians, April 23, 1941

They constitute two members of a series which may well include additional representatives, for example with similar side-chains having 10 and 15 carbon atoms, but such substances have not as yet been encountered in nature. Vitamin K_1 alone has been produced synthetically. Fortunately, a comparatively simple method is available for the production of the compound in a pure form from methyl-naphthohydroquinone and phytol⁶. Thus pure, synthetic 2-methyl-3-phytyl-1,4-naphthoquinone, which is identical in every respect with natural vitamin K_1 isolated from alfalfa, is the only true vitamin factor available for use as a therapeutic agent.

Another common misconception is that significant vitamin K activity is exhibited by a large number of simple quinones. Much depends upon what is considered to be "significant activity," but I should say that a substance to merit any consideration as a possible therapeutic agent certainly should possess at least one twenty-fifth the activity of vitamin K_1 . Among a large number of quinones of diversified types which have been investigated, this criterion is met by only a very small group of naphthoquinones derived from or related to vitamins K_1 and K_2 . The early note by Almquist and Klose⁹ announcing that phthiocol possesses antihemorrhagic activity was justly acclaimed as an interesting discovery, for this was the first indication that substances other than the natural vitamins can exhibit this type of biological property. At present, however, it is recognized that phthiocol possesses only very feeble activity, being no more than about one five-hundredth as active as vitamin K_1 ,¹⁰ and the substance has been dropped from consideration as a possible drug. The list of quinones possessing significant activity, as defined above, includes only the actual vitamins and their immediate derivatives, 2-methyl-1,4-naphthoquinone, which represents a component part of the vitamin K_1 and K_2 molecules, and three substances differing from vitamin K_1 only in having, in place of the phytyl group, the comparable but shorter hydrocarbon substituents farnesyl, geranyl, and cinnamyl¹⁰.

Indeed, contrary to preliminary indications, a high degree of specificity exists in the chemical structures of the natural vitamins. This can be seen from an inspection of the chart in figure 2, which summarizes some of the data accumulated in a comprehensive investigation of the relationship between vitamin K activity and structure¹⁰. By suitable processes of synthesis or of chemical transformation, about every conceivable modification of the vitamin K_1 molecule has been investigated, and in every instance the change is attended with a distinct diminution in biological potency. Such slight alteration as the addition of two hydrogen atoms, which changes the molecular weight only from 451 to 453, results in a 4- to 8-fold loss, depending on where the hydrogens are attached, while the addition of a CH_3 group, which changes the molecular weight by only 3 per cent, practically or wholly deactivates the molecule.

2-Methyl-1,4-naphthoquinone appears to constitute a single exception, for it is a highly active quinone¹¹ and yet, in contrast to the vitamins, which have at the 3-position a side-chain which is highly specific with respect to

Diagram illustrating the chemical transformations of 1,2-dimethyl-1,4-cyclohexadiene-5-carboxylic acid (the central structure) and the associated fold losses:

- Addition of CH_3** (Complete Loss) leads to a structure with a methyl group at position 4.
- Addition of 2 H-atoms** (8-Fold Loss) leads to a structure with a methyl group at position 3.
- Removal of CH_3 -groups** (5-9 Fold Loss) leads to four structures with methyl groups at positions 3, 4, 6, and 7.
- Hydrogenation** (4-125 Fold Loss) leads to a structure with a methyl group at position 6.
- Removal of CH_3** (50-Fold Loss) leads to a structure with a methyl group at position 7.
- Change to CH_2CH_3** (1000-Fold Loss) leads to a structure with an ethyl group at position 3.
- Shortening of Chain** (25-Fold and 5-Fold Loss) leads to a structure with a methyl group at position 3.

Fig 2 Specificity of the vitamin K₁ structure Loss in activity attending alterations in the vitamin K₁ molecule

phytol to give vitamin K₁ while similar substances might well arise from a synthesis occurring in the liver utilizing vitamin A or a carotinoid pigment. Such a biosynthesis, which would entail a 3- or 4-fold increase in the molecular weight, would account for the anomalously high potency of the simple compound on a weight basis in the chick test. Further possible courses of the biosynthesis will be mentioned below.

I should like to dwell on the question of what happens to the administered material, because I think that this may be not merely a matter of academic interest but one which has a direct bearing on the choice of drugs for hypoprothrombinemia therapy. Although a rather confusing array of individual substances has been proposed, the choice really lies between one or the other of just two types. One of these comprises synthetic vitamin K₁, its oxide,²⁰ and hydroquinone diphosphate,¹⁰ and possibly the analogous 2,3-disubstituted

naphthoquinone described below, the other is that of 2-methyl-1,4-naphthoquinone and its derivatives and congeners. Some of the substances of the second type are illustrated in figure 3. The reduced form, or hydroquinone, is too sensitive to oxidation to be used as such, but it can be employed as the water-soluble diphosphate¹² or disuccinate¹³. A water-soluble sodium bisulfite complex of unknown structure¹⁴ is also active. The methylnaphthol¹⁰ and methylaminonaphthol^{15, 18} shown in the formulas probably undergo bio-oxidation to methylnaphthoquinone. The hydroquinone diphosphate and disuccinate likewise are probably transformed into the quinone in the organism.

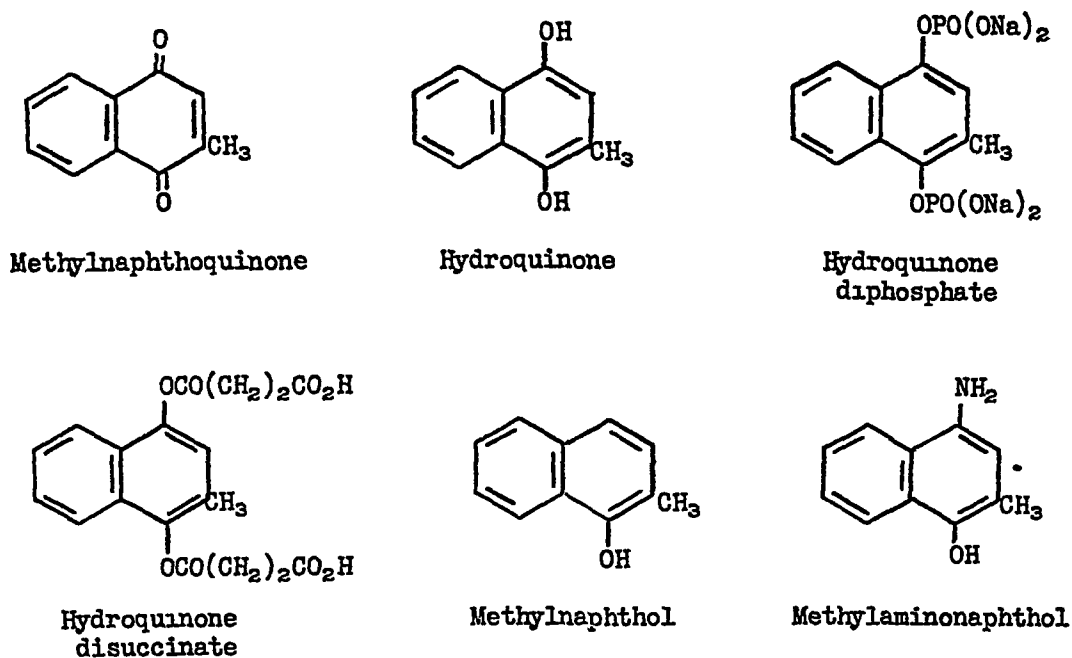


FIG 3 2-Methyl-1,4-naphthoquinone and related compounds

Since each series apparently comprises a group of biologically equivalent individual derivatives, the question of prime importance in the selection of a preferred drug resolves itself into a choice between synthetic vitamin K₁ and methylnaphthoquinone. Other things being equal, it would seem reasonable to give preference to a substance identical with a natural vitamin. Certain purveyors of pharmaceutical products have confused the issue for the physician by offering methylnaphthoquinone under the designation "synthetic vitamin K". This is entirely false. Methylnaphthoquinone is a substitute compound, but it certainly merits consideration as such if it is capable of giving good service. This is the question which I should like to consider in more detail.

One disadvantage of methylnaphthoquinone is that it possesses a certain toxicity not encountered in the vitamin. When given orally to rats and mice,

methylnaphthoquinone is lethal at dosages of 0.35–0.5 g per kg, whereas vitamin K₁ shows no lethal effect even in amounts up to 25 g per kg¹⁶. The toxic dose of the substitute compound assuredly is so far removed from the therapeutic dose that no actual danger is likely to be involved in its use, but, nevertheless, the toxic character is a definite disadvantage. Those who have worked much with the compounds in the chemical laboratory are well aware that methylnaphthoquinone is a skin irritant while vitamin K₁ is entirely innocuous. Methylnaphthohydroquinone is a notable sternutator.

The fact that methylnaphthoquinone is more potent than vitamin K₁ in the chick assay might at first appear to constitute an advantage for the substitute compound. The relative responses evoked by the two substances in chicks, however, afford no adequate basis for predicting the ratio of effectiveness to humans. Many examples exist of a profound differential in the response of different species to different compounds (e.g., vitamin D₃ and calciferol given to chickens, rats and humans, testosterone and androsterone in the capon and rat assays). Certainly the results of animal experiments with drugs cannot be translated directly in terms of human therapy. The question of the relative therapeutic efficacy of the two agents is a matter for clinical investigation. Results of careful clinical comparisons made by Seligman, Hurwitz, Frank and Davis¹⁷ indicate that no great disparity exists in the weight of vitamin K₁ and methylnaphthoquinone required to produce a satisfactory therapeutic response. It is by no means necessary or advisable to triple the dose of vitamin K₁ over that of the simple quinone merely on the basis of chick assays conducted with a standardized 18-hour period of observation. Indeed Seligman and co-workers find that vitamin K₁ has such a persistent and prolonged action that a single small dose is adequate for the treatment of even severe cases of hypoprothrombinemia and may well do the work of repeated dosage with other agents. From direct comparisons of several compounds, they conclude that "a single 10-milligram dose of vitamin K₁ given intravenously in cases of obstructive jaundice and biliary fistula produced a more rapid and prolonged effect than any other substance so far reported."

The strikingly contrasting chemical properties of vitamin K₁ and methylnaphthoquinone afford an interesting interpretation of the persistence and lack of toxicity of the former agent, as compared with the latter. Vitamin K₁ may be characterized as a stable, chemically inert substance, whereas methylnaphthoquinone is extremely reactive and tends to combine with a wide variety of reagents. The difference is understandable chemically, for methylnaphthoquinone has a free 3-position with a hydrogen atom capable of being replaced by substituents, in vitamin K₁ this position is blocked by the long phytyl group, which thus has a protective function. The contrast is clearly demonstrated by adding a solution of ethyl cyanoacetate in alcoholic ammonia to dilute solutions of methylnaphthoquinone and vitamin K₁, when a striking, deep blue color is produced in the former case and no change oc-

curs in the latter. The reagent used, to be sure, is quite foreign to the body, and this test is merely illustrative of a contrast in the properties. However, substances of the same type as ethyl cyanoacetate occur in the body and conceivably may combine with administered methylnaphthoquinone. One such substance is acetoacetic acid, which arises in the organism as a product of β -oxidation, and a test shows that this compound, in the form of the ester, gives a marked color reaction with methylnaphthoquinone but not with vitamin K₁ (table 1). Pyruvic acid, another biological product which

TABLE I

Color Reactions

(Tests made with 5 cc portions of 0.5 per cent solutions)

Reagent added	2-Methyl-1,4-naphthoquinone Color (after 2 days)	Vitamin K ₁
None	Light yellow	Light yellow
Ethyl cyanoacetate ¹	Intense blue (rapid)→brown	No change
Ethyl acetoacetate ¹	Deep red-brown	No change
Pyruvic acid ¹	Red-brown	No change
Aniline - (1 drop)	Orange-red	No change
Ethanolamine (1 drop)	Brown→deep red	Sl. brownish
Lysine ³	Light orange-brown (slow)	No change
Thioglycolic acid (1 drop)	Deep yellow	No change
Cysteine ⁴	Deep cherry red (rapid)	No change

¹One drop of reagent, in a solution of 1.5 cc of alcohol and 0.5 cc of concentrated ammonia solution. This amount of alcoholic ammonia itself produces a discoloration, but the color change is considerably slower and much less intense than that arising in the presence of the reagent indicated. An improved test reagent for the detection of methylnaphthoquinone is prepared by dissolving 200 mg of anhydrous sodium acetate in 1 cc of water and adding 9 cc of 95 per cent alcohol and 0.2 cc of ethyl cyanoacetate. When 0.5 cc of this reagent solution is added to 5 cc of an alcoholic solution of methylnaphthoquinone, a clear and persistent blue color appears and reaches maximum intensity in one-half to one hour. A faint but distinct color is observable in a solution containing 10 γ of methylnaphthoquinone per cc.

²The color reaction with dimtrophenylhydrazine described by Novelli (Science, 1941, *vol.* 81, 357) is applicable to 2-methyl-1,4-naphthoquinone but not, as this author implies, to vitamin K₁. I have made trials with a large amount of the vitamin and an extended period of heating, with only negative results.

³An aqueous solution of 44 mg of lysine dihydrochloride and two equivalents of sodium acetate, diluted to 4 cc with alcohol.

⁴A solution of 100 mg of cysteine hydrochloride and 50 mg of sodium acetate in 5 cc of water was diluted with 15 cc of alcohol and the solution filtered from precipitated salt, 2 cc of this filtrate were used in each test.

also may be described as an active-hydrogen keto acid, gives a similar response. It is interesting to inquire into the possibility of other combinations in the body. Methylnaphthoquinone, in contrast to vitamin K₁, combines readily with amines foreign to the organism, such as aniline, and it also reacts with ethanolamine, the parent substance of choline. A slow but distinct reaction is noted with the amino acid lysine, probably due to a combination involving the ϵ -amino group, and this indicates the possibility that the administered quinone may combine similarly with the lysine units of proteins.

A still more striking and rapid reaction occurs with sulfhydryl compounds, of which thioglycolic acid constitutes a non-biological model. The reaction has been studied in our laboratory¹⁸ and found to proceed readily and to yield a beautifully crystalline product (figure 4). The compound is almost as active in the chick assay as vitamin K₁, it is even more stable than this substance, its sodium salt is water soluble, and indeed the compound offers promise of being a valuable therapeutic agent. A similarly rapid reaction occurs with the natural amino acid cysteine, giving a highly pigmented product which is under investigation. One would expect glutathione to behave similarly. In consideration of the rapidity of the reaction, as compared with that with lysine, it is likely that methylnaphthoquinone can

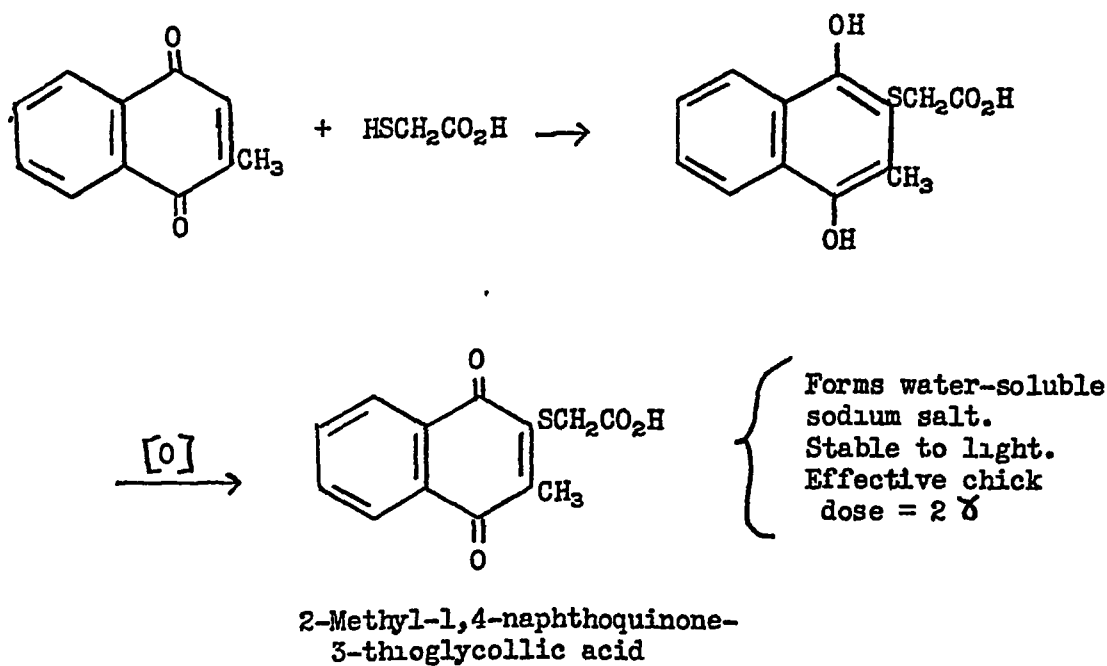


FIG 4 Reaction with a sulfhydryl acid

combine with proteins most readily by utilization of the sulfhydryl groups rather than the ϵ -amino groups.

In view of this array of reactions which can occur under mild conditions, it seems hardly possible that methylnaphthoquinone administered to the animal body can escape some form or forms of alteration. Some of the possible transformations are indicated in figure 5. As mentioned above, the possibility exists that some of the material may combine with an alcohol of the phytol or vitamin A type, and afford a product of the actual vitamin K type. At the other extreme, it may in part undergo hydroxylation to phthiocol, for this reaction is easily realized in the laboratory¹⁰. Since this product is but feebly active, such a process would entail an effective diversion of the therapeutic agent. The result of the other possible transformations cannot be evaluated, for not enough is known about the properties of the possible

products. The fact that the thioglycollic acid derivative mentioned above is highly active suggests that at least some of the products of the reaction of methylnaphthoquinone with natural amino acids may possess antihemorrhagic activity.

This picture is not very favorable to the use of methylnaphthoquinone in therapy. The substance evidently can enter into some of the favorable forms of transformation, but the extent to which dissipating side reactions also occur remains in question. Consideration also should be given to the possible toxic, or otherwise undesirable, characteristics which may be associated with conjugates resulting from administered methylnaphthoquinone. The fate and action of the administered material would appear to be subject

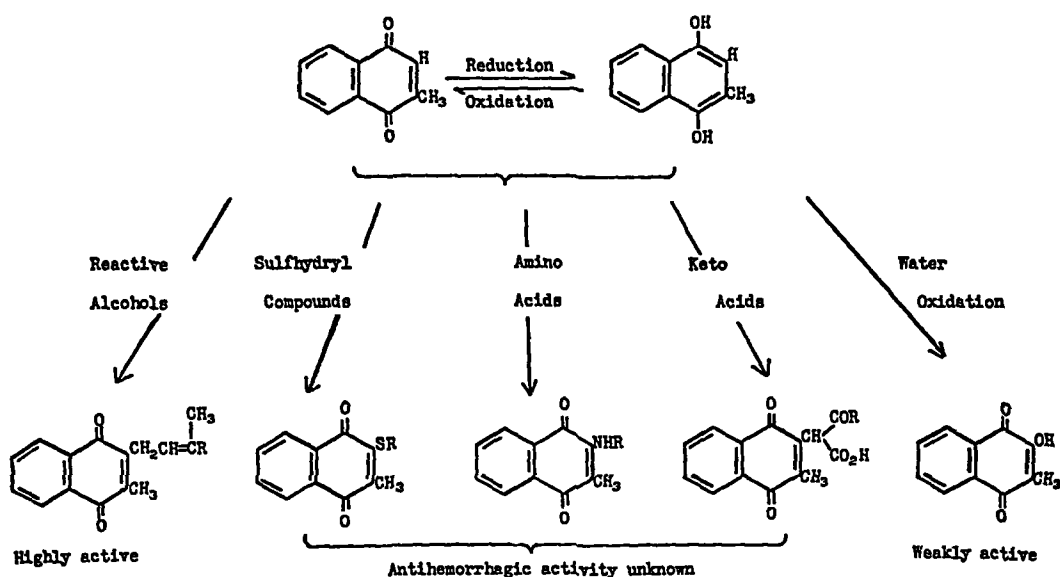


FIG 5 Possible transformations of methylnaphthoquinone in the body

to considerable uncertainty, and the wide opportunity for transformations of different types would lead one to expect a variability in the response, dependent upon the site and mode of administration and the condition of the patient.

These chemical considerations, which coincide with clinical findings, indicate that the stable, unreactive vitamin K_1 is a safer and surer agent for hypoprothrombinemia therapy, and one capable of persisting and exercising control over a prolonged period. The only precaution necessary in employing vitamin K_1 is to avoid exposure to light, for the substance is highly photosensitive, a property shared with methylnaphthoquinone. The sensitivity to light necessitates careful handling of the vitamin and is a definite if not a prohibitive disadvantage to its use as a drug. Fortunately this one defect can be obviated by using in place of synthetic vitamin K_1 an oxide derivative which appears to be biologically equivalent to the vitamin and

which is easily obtainable from and convertible into this substance Vitamin K_1 oxide²⁰ is a colorless, or very nearly colorless oil, which, like the yellow vitamin, is soluble in alcohol and insoluble in water (figure 6) It shows no particular sensitivity to ordinary light, either alone or in solution, and requires no special handling The oxide is even more stable and inert chemically than the parent vitamin In the chick assay the oxide and vitamin are practically indistinguishable in antihemorrhagic activity, and Drs Seligman, Hurwitz and Frank have informed me that they have obtained excellent clinical results with vitamin K_1 oxide

Considerable interest has centered around the use in parenteral therapy of the various water-soluble derivatives of methylnaphthohydroquinone of the types mentioned above However, the water-insoluble vitamin K_1 can be given satisfactorily, and indeed very effectively, in the form of an aqueous emulsion, with retention of all of the advantages noted The remarkable dispersive quality of vitamin K_1 was observed by Dr A M Seligman and

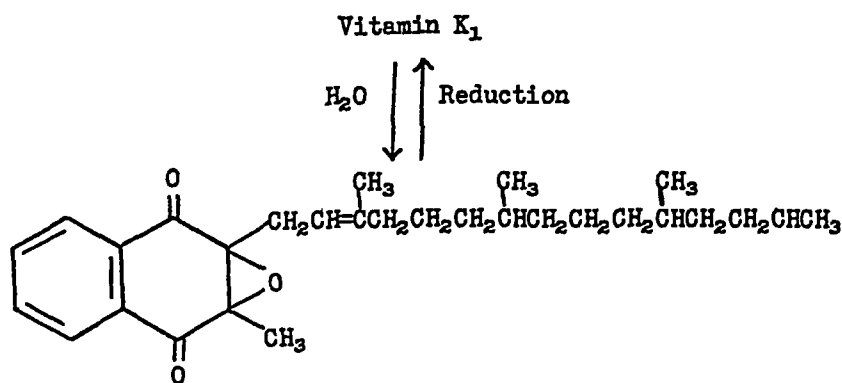


FIG 6 Vitamin K_1 oxide

utilized by him and his collaborators in the development of a very simple and satisfactory technic of vitamin K therapy²¹ The same investigators, in unpublished work which they have kindly permitted me to mention, have found that vitamin K_1 oxide likewise forms very stable emulsions Initially, the emulsions were prepared by dispersing 10 mg of the oily vitamin or oxide in 1 liter of 10 per cent glucose solution, but in the more recent work it has been found that the large volume of water is not necessary A dispersion of 10 mg of vitamin K_1 oxide in 15 c c of solution has been employed clinically with distinct success, for example, the intravenous injection of this emulsion promptly reduced the prothrombin clotting time of a patient from 90 to 19 seconds The emulsions are prepared by the very simple expedient of mixing an alcoholic solution of vitamin K_1 or its oxide with a suitable volume of glucose or saline solution and shaking the mixture for a minute or two The dispersion mentioned above was prepared from a solution of 10 mg of the oxide in 3 c c of alcohol and 12 c c of glucose solution, but the proportions can be varied over a considerable range Thus the volume of

glucose solution can be decreased to 7 c c satisfactorily. Emulsions containing as much as 10 mg of the oxide in 10 c c of solution are smooth, bluish white suspensions containing no visible oily droplets, and those that I have prepared have shown no sign of separation over a period of five months. The suspensions can be autoclaved, and may prove to remain in a dispersed condition for prolonged periods. Dr Seligman suggests that perhaps the most convenient procedure is to autoclave a suitable volume of the alcoholic solution of the oxide and, when an emulsion is required, to draw this into sterile glucose or saline solution in a syringe and shake the mixture prior to injection.

With the introduction of vitamin K₁ oxide and the development of this simple technic of preparing emulsions, it appears that the physician has at his disposal a practically ideal agent for vitamin K therapy.

BIBLIOGRAPHY

- 1 DAM, H. Cholesterinstoffwechsel in Huhnereiern und Huhnchen, *Biochem Ztschr*, 1929, ccxv, 475-492
- 2 DAY, H., GEIGER, A., GLAVIND, J., KARRER, P., KARRER, W., ROTHSCCHILD, E., and SALOMON, H. Isolierung des Vitamins K in hochgereinigter Form, *Helvet Chim Acta*, 1939, xii, 310-313
- 3 MCKEE, R W., BINKLEY, S B., MACCORQUODALE, D W., THAYER, S A., and DOISY, E A. The isolation of vitamins K₁ and K₂, *Jr Am Chem Soc*, 1939, lxi, 1295
- 4 BINKLEY, S B., CHENEY, L C., HOLCOMB, W F., MCKEE, R W., THAYER, S A., MACCORQUODALE, D W., and DOISY, E A. The constitution and synthesis of vitamin K₁, *Jr Am Chem Soc*, 1939, lxi, 2558-2559
- 5 FIESER, L F. Synthesis of 2-methyl-3-phytyl-1,4-naphthoquinone, *Jr Am Chem Soc*, 1939, lxi, 2559-2561, also Identity of synthetic 2-methyl-3-phytyl-1,4-naphthoquinone and vitamin K₁, *Jr Am Chem Soc*, 1939, lxi, 2561
- 6 FIESER, L F. Synthesis of vitamin K₁, *Jr Am Chem Soc*, 1939, lxi, 3467-3475
- 7 MACCORQUODALE, D W., CHENEY, L C., BINKLEY, S B., HOLCOMB, W F., MCKEE, R W., THAYER, S A., and DOISY, E A. The constitution and synthesis of vitamin K₁, *Jr Biol Chem*, 1939, cxlxi, 357-370
- 8 MCKEE, R W., BINKLEY, S B., THAYER, S A., MACCORQUODALE, D W., and DOISY, E A. The isolation of vitamin K₂, *Jr Biol Chem*, 1939, cxlxi, 327-344
- 9 ALMQUIST, H J., and KLOSE, A A. The antihemorrhagic activity of pure synthetic phthiocol, *Jr Am Chem Soc*, 1939, lxi, 1611
- 10 FIESER, L F., TISHLER, M., and SAMPSON, W L. Vitamin K activity and structure, *Jr Biol Chem*, 1941, cxxxvii, 659-692
- 11 ANSBACHER, S., and FERNHOLZ, E. Simple compounds with vitamin K activity, *Jr Am Chem Soc*, 1939, lxi, 1924-1925
- 12 FIESER, L F., and FRY, E M. Water-soluble antihemorrhagic esters, *Jr Am Chem Soc*, 1940, lxi, 228-229
- 13 DAM, H., GLAVIND, J., and KARRER, P. Die biologische Aktivitat der natuerlichen K-Vitamine und einiger verwandter Verbindungen, *Helvet. Chim Acta*, 1940, xxiii, 224-233
- 14 RIEGEL, B. Vitamin K, *Ergebn d Physiol*, 1940, xliii, 169
- 15 EMMETT, A D., KAMM, O., and SHARP, E A. The vitamin K activity of 4-amino-2-methyl-1-naphthol and 4-amino-3-methyl-1-naphthol, *Jr Biol Chem*, 1940, cxlxi, 285-286

- 16 MOLITOR, H, and ROBINSON, H J Oral and parenteral toxicity of vitamin K₁, phthiocol and 2-methyl-1,4-naphthoquinone, *Proc Soc Exper Biol and Med*, 1940, xliii, 125-128
- 17 SELIGMAN, A M, HURWITZ, A, FRANK, H A, and DAVIS, W A The intravenous use of synthetic vitamin K₁, publication in press
- 18 FIESER, L F, and TURNER, R B, unpublished work
- 19 FIESER, L F Convenient procedures for the preparation of antihemorrhagic compounds, *Jr Biol Chem*, 1940, cxxxiii, 391-396
- 20 TISHLER, M, FIESER, L F, and WENDLER, N L Hydro, oxido and other derivatives of vitamin K₁ and related compounds, *Jr Am Chem Soc*, 1940, lxi, 2866-2871
- 21 FRANK, H A, HURWITZ, A, and SELIGMAN, A M The treatment of hypoprothrombinemia with synthetic vitamin K₁, report of two cases, *New England Jr Med*, 1939, ccxxi, 975-977

THE STATE OF SENSORY AND MOTOR CENTERS IN PATIENTS WITH HYPOTHYROIDISM *

By NORBERT ENZER, M D , F A C P , ERNST SIMONSON, M D , and SAMUEL
S BLANKSTEIN, M D , *Milwaukee, Wisconsin*

INTRODUCTION

INCREASED fatigability and sluggishness are notable complaints and symptoms of patients with endocrine disturbances, particularly in those with a reduced metabolic rate. Since increased fatigability results also from mental work and is present even under resting conditions in these patients it occurred to us that it might be due to an impairment of some functions of the central nervous system. The metabolism of nerve tissue, like that of other tissues, is influenced and regulated by hormonal factors, particularly when oxygen utilization is affected. Disturbances of nervous functions are, therefore, to be expected when there are pathological alterations in the endocrine system. It appears probable that nerve cells cannot maintain their normal excitability if their metabolism is diminished or altered. It seems important to know if fundamental functions of the central nervous system are impaired in patients with endocrine disturbances.

For this investigation we chose simple methods, applicable in clinical laboratories. As an example of a sensory function we chose the flicker phenomenon. The fusion frequency of flicker is that rate of successive light stimuli at which the sensation of flickering disappears and becomes the same as continuous illumination. The fusion frequency of flicker depends on chronaxie, latent period and refractory period of the retina, the nervous pathways, and the visual centers. Since in any measurement of sensory functions it is difficult to differentiate between sensory receptor organ and center, it is probably more appropriate to speak of the retino-cortical system.

The retina, however, is regarded by many authors (for bibliography see Granit ¹) as a projected part of the central nervous system, and Elsberg and Spotnitz ² recently showed similarities in fundamental retinal responses to general laws of excitation and inhibition established by Sherrington on the flexor reflex. Therefore, it may be assumed that such general disturbances as decreased metabolism would affect visual centers as well as the retina. In any case, the fusion frequency of flicker is regarded as a fundamental visual function (Hecht, ³ Crozier ⁴). We found that the fusion frequency of flicker is decreased in fatigue of the central nervous system produced by occupational work (such as typing, secretarial work, laboratory work, etc ⁵). A decrease of fusion frequency in patients in the resting condition, therefore, would explain a decreased resistance against fatigue.

* Received for publication November 19, 1940

From the Research Laboratory of the Mount Sinai Hospital, Milwaukee, Wisconsin

The motor function may be subdivided into absolute muscular force (strength), endurance, speed and skill (McCurdy⁶) These functions concern different processes, they may be increased by training independently of one another As sluggishness is the prevailing symptom of many patients with decreased metabolic rate, the measurement of maximum speed of movements would seem to be important and informative

It is known that many motor impulses are necessary for the accomplishment of one voluntary movement The smaller the leg and the less the inertia, the greater is the possible maximum frequency of movements, and the closer this maximum would be to the actual frequency of motor discharges in the centers Lehmann⁷ has shown that there is a close relationship between the frequency of finger movements and the frequency of impulses in the motor centers, so that it is possible to calculate the motor frequency of the centers from an analysis of finger movements In fatigue of normal subjects, the time of discharge is lengthened and thus the frequency is diminished

For these reasons the measurement of the maximum speed of finger movements was chosen for study of the state of motor centers The frequency of finger movements can be related only to the function of the motor centers, because no other peripheral physiological function is involved demanding any considerable increase of respiration, circulation or metabolism In connection with this it may be mentioned also that the fatigue in working with the finger-ergograph is due to fatigue of the motor or sensory centers as shown by Mosso, who produced muscular contractions by electrical stimulation applied immediately after complete voluntary fatigue The maximum speed of finger movements as well as its drop was measured during a one minute performance

Thirteen patients with decreased metabolic rate and with a diagnosis of primary or secondary hypothyroidism were studied Among them were two patients with outright myxedema and one patient with symptoms of myxedema All of them were treated with thyroid preparations In table 1 the minimum value of the metabolic rate is indicated as well as the last value taken a few days before our experiments Most of the patients (cases 1, 3, 4, 5, 6, 7, 9, 11) were overweight or had a tendency to gain weight The most uniform feature of this group of patients was the increased blood cholesterol content (between 202.4 and 490.0 mg per cent) The cholesterol content was not determined in case 3 (myxedema), cases 4 and 1 were included although their metabolic rate was normal, because both were obese women with premature (4) or artificial (1) menopause The normal range of the basal metabolic rate is rather wide, therefore, a normal value does not necessarily exclude some hypofunction of the thyroid gland

TABLE I
Fusion Frequency and Motor Frequency in Patients with Hypothyroidism

Pat no	Sex	Age	Diagnosis	Decrease of BMR in % of normal stand		Tendency to over-weight	Bl chol-esterol in mg %	Fusion frequency flashes per sec	Max motor frequency impulses per 10 sec	No of decreased max or min values of motor frequency out of a total no of 8 values
				Min	Last month					
1	F	43	Artificial menopause	-5 0	-5 0	+	282 5	37 6, 35 8	45, 43	7
2	F	37	Myxedema	-22 2	-11 7	-	490 0	36 8	47	8
3	M	36	Myxedema	-39 4	-39 4	+	—	32 8	34 0	8
4	F	33	Menstr ceased, gained 90 lbs during last wks	—	—	+	—	35 4, 35 0	—	—
5	F	15	Hypothyroid symptoms of myxedema	—	+6 5	+	223 0	37 6	70	1
6	F	54	Hypothyroid, hypertension bl pressure 190/110	-25 0	-25 0	+	250 0	33 6	34	2
7	F	39	Hypothyroid	-10 6	-8 0	+	232 6	33 6	72	3
8	F	34	Hypothyroid	-10 5	-9 3	+	234 7	40 8, 40 8	43	3
9	F	50	Hypothyroid	-24 9	-21 3	-	228 4	38 4	65	—
10	M	47	Hypothyroid	-21 7	-21 7	+	282 5	40 0	65	—
11	F	46	Hypothyroid	-20 5	-20 5	-	224 1	35 2, 34 8	57	1
12	F	56	Hypothyroid, hypertension bl pressure 170/110	-12 2	-10 3	+	394 1	34 8, 34 4	53, 53	6
13	F	50	Hypothyroid	-22 8	-22 8	-	409 8	33 2, 36 0*	46, 51*	6, 5*
				-29 1	-29 1	-	202 4	36 6	60	2

* Condition unimproved

METHODS

We used a known rotator arrangement where the beam of light from an electric bulb (25 watt Mazda) was interrupted by a rotating disk with four identical openings. The subject was seated with his head placed on a chin rest so that the distance from the illuminated area to the eye was kept constant at one meter. The speed of the motor was increased until fusion occurred. The number of rotations was measured by a revolution counter and a stop watch. The subjects were examined under the following standard conditions: the vertical intensity of illumination of the surrounding field at the plane of the illuminated area was two foot-candles, the size of the illuminated area was 100 sq mm, equivalent to a visual angle of $\frac{1}{2}$ degree. The relation of the four openings (flashes) of the rotating disk to the dark intervals was 64:36, i.e. 64 per cent of the whole cycle. The intensity of illumination of the test patch was 0.0039 candle power per sq cm. Binocular central vision was used. Our results concern the fovea exclusively. The time of exposure was 1.5 sec. The accuracy with which the values can be reproduced is high, the variation of the values, taken in the same experiment does not exceed 1 or 2 cycles per sec. The daily variations do not exceed, as a rule, 3 to 4 cycles, provided that the subject's condition is the same.

For the maximum frequency of finger-movements the following method was used: the patient stood in front of a Cenco Impulse Counter, placed on a table. He was asked to press the button with his middle finger as fast as he could do it, until the stop signal was given, after one minute performance. After one minute pause, the test was repeated. First the right hand was examined and then the left hand in the same way. During the performance the number of contacts per each 10 seconds was counted by means of a stop watch. Thus the frequency is given in number of impulses per 10 seconds. The frequency drops during the performance from an initial high value (maximum) in a more or less irregular way so that the minimum value may occur as well in the last 10 seconds, as in the 30-40th, or 40-50th second.

The individual performance is characterized by the initial value (maximum) and by the minimum to which it drops independently of where it occurs during the performance. The difference between maximum and minimum values obviously is due to the fatigue of the motor centers during the performance. As the test is performed twice for each hand, we obtain 4 maximum and 4 minimum values as criteria of the performance.

In experiments on 45 normal subjects the daily variations were almost negligible; for instance for the initial (maximum) value of the right hand in the first performance they did not exceed 2 impulses per 10 seconds.

RESULTS

Table 1 shows the values of fusion frequency (column 9). The three values in case 1, and the two values in cases 3, 7, 10, 11, and 12 concern

different examinations on different days. The fusion frequency of these patients is as remarkably constant as we have found in normal subjects. The higher value of the second examination in case 12 coincides with an improved condition of this patient. The lowest value of 45 normal subjects was 40.0 flashes per second, the normal average was 45.0. All values of the patients are below the normal mean value 45.0. The values of cases 7 and 8 are identical with the lowest normal value. It is probable that they are decreased. The values of the other 12 patients are lower than the lowest normal value, in these cases there is a definite pathological decrease. The decrease of fusion frequency is most pronounced in the cases with myxedema, 2, 3 and 5. In cases 6 and 12 the very low value may be due in part to hypertension. We have found in another series of experiments that the fusion frequency is diminished in patients with hypertension. The mean value of the whole group is 36.3, compared with the normal mean value of 45.0. The vision of our patients was normal or corrected to normal. The results show a definite decrease of fusion frequency in these patients.

Table 1, column 10, shows the values of the maximum (initial) frequency of finger movements per 10 sec. for the first performance with the right hand. The lowest normal value of a group of 45 subjects was 59, the mean value was 69.7 impulses per 10 sec.

Two patients (cases 4 and 6) showed values higher than the normal average, and in eight patients the values were lower than the lowest normal value. The average of all patients was 56.8, compared with the normal average of 69.7. The difference between the normal subjects and the group of patients is still more manifest, if all eight maximum and minimum values are considered. Column 11 shows the number of pathologically decreased maximum or minimum values, i.e. of values lower than the lowest corresponding normal value. With the exception of only two cases (cases 8 and 9) at least one of the values is lower than the corresponding lowest normal value. In the myxedema patients, cases 2 and 3, all eight values were pathologically decreased. Case 3 was not able to carry through the performance, therefore the exact minimum could not be determined, but there is no doubt that all eight values were considerably lower than the lowest normal values.

The drop of motor frequency during the performance indicates the fatigability of motor centers. We found in our 45 normal subjects that the drop of frequency depends on the initial frequency in a straight-lined function, the higher the initial frequency the greater is the drop during the performance. Figure 1 shows this relationship for the first performance of the right hand (ordinata = drop of frequency, abscissa = initial frequency). The values of all patients lie above the full line, with the exception only of case 10, that means that the drop of frequency is greater than in the normal subjects. The fatigability of motor centers in our patients is increased and it is interesting that this weakness of motor centers is very pronounced in cases 4, 6, 7, and 8 who showed a normal initial frequency.

There is no correlation between the decrease of fusion frequency or the frequency of motor impulses and the diminution of basal metabolic rate or cholesterol content of the blood. There is no relationship between the decrease of fusion frequency of flicker and the frequency of motor impulses, although both functions are diminished.

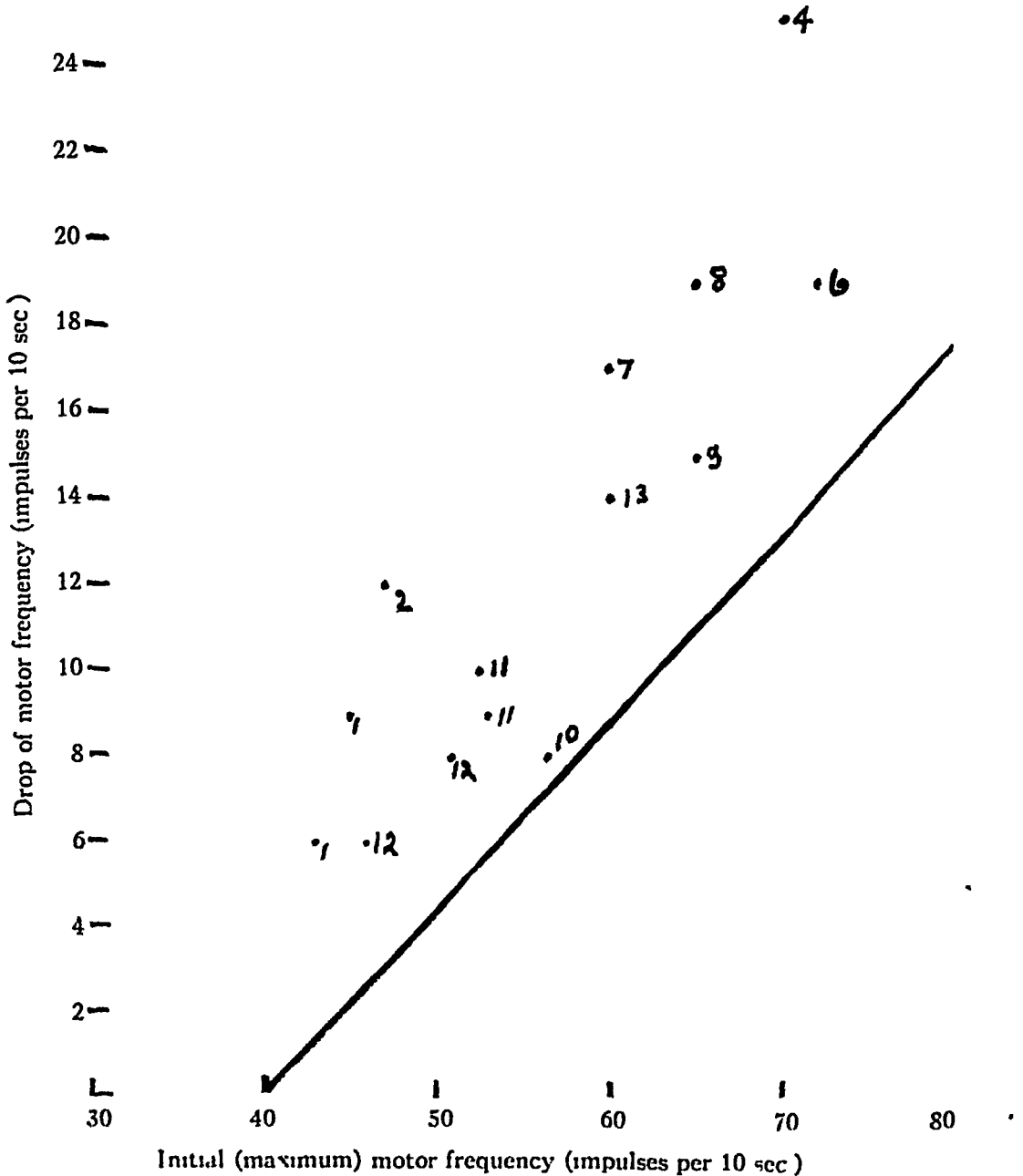


FIG 1 Drop of motor frequency during the performance (right hand) dependent on the initial value in normal subjects (drawn in full line average of 45 subjects) and of patients with hypothyroidism

The studies of Bertrand et al⁸ on the electroencephalogram in seven patients with myxedema corroborate our findings. These authors found a diminution of the amplitude slow large waves with a frequency of 3 to 4

per second, absence of the Berger-rhythm and, what is especially interesting with regard to our results, absence of the reaction to visual stimuli. As in our experiments, there was no direct relationship between these changes of the electroencephalogram and the diminution of the basal metabolic rate.

CONCLUSIONS AND SUMMARY

The experiments show that the state of sensory (determined by the fusion frequency of flicker) as well as that of motor centers (determined by the maximum frequency of finger movements) is deteriorated in patients with disturbances of the endocrine system characterized by diminished metabolic rate and increased blood cholesterol content. In some patients the decrease of fusion frequency, in other patients the decrease of motor frequency is more pronounced. Eleven of 13 patients have values of fusion frequency lower than the lowest value of 45 normal subjects, the other two have values that coincide with the lowest normal values. These results explain the disposition to increased fatigability of those patients, as the fusion frequency of flicker is diminished in nervous fatigue. The weakness of motor centers is shown by the increase of the drop of frequency during the performance.

REFERENCES

- 1 GRANIT, R. Die Elektrophysiologie der Netzhaut und des Sehnerven, Acta Ophth, 1936, xiv, Suppl. viii, 1.
- 2 ELSBERG, A. CH., and SPOTNITZ, H. The sense of vision. III. A theory of the functions of the retina, Bull. Neurol. Inst. New York, 1937, vi, 253.
- 3 HECHT, S. The nature of the visual processes, Bull. New York Acad. Med., 1938, xiv, 21.
- 4 CROZIER, J. W. On the sensory discrimination of intensities, Proc. Nat. Acad. Sci., 1936, xii, 412.
- 5 SIMONSON, E., and ENZER, N. Influence of fatigue on the fusion frequency of flicker, Jr. Indust. Hyg., 1941, xxiii, 83.
- 6 MCCURDY, J. H. The physiology of exercise, 1939, Philadelphia.
- 7 LEHMANN, G. Ueber den Mechanismus der Willkuerbewegung, Arbeitsphysiologie, 1928, i, 1.
- 8 BERTRAND, F., DELARY, J., and GUILLAIN, J. L'Électroencephalogramme dans le myoedeme, Compt. rend. Soc. d. biol., Paris, 1938, cxxix, 395.

THE CONCEPT OF PSYCHOSOMATIC RHEUMATISM *

By JAMES L. HALLIDAY, M.D., *Glasgow, Scotland*

The results of psychological, particularly medical psychological investigation, pass through three stages of opposition, like a bill in Parliament. At the first reading they are said to be absolutely untrue, at the second reading, they are said to be abnormal and improper, at the third reading they are said to be trivialities well-known to everybody since the Flood —DR. MAJOR GREENWOOD

How do we differentiate between "true fibrositis" and "psychoneurotic rheumatism"? Before attempting to answer this question it is wise to consider the meaning usually attached to each of these terms

DEFINITIONS

Fibrositis This word stands for the idea that subjective complaints of localized pain and stiffness can commonly be related to localized objective findings such as nodules, thickenings and indurations which result from inflammation of fibrous tissue and fascia. The objective existence of these nodules, etc., can be demonstrated by palpation, and also by pathological examination. The etiology is obscure, but many consider that these abnormal formations are dependent on focal infections. Others, however, have maintained that they are secondary to metabolic upsets, whether dietetic or endocrine. Massage, especially if deep and if it hurts the patient, will in course of time rub away or liquify these nodules, and with this there is disappearance of the symptoms. This is a pleasantly simple theory, but there are certain objections to it. For example

1. Enthusiasts for fibrositis have claimed that they are able to palpate nodules in a very large percentage of patients who are in common language said to be suffering from "rheumatism" (non-arthritis), both by the laity and by the medical profession. To such enthusiasts, the problem of non-arthritis is already solved. Unfortunately, many physicians, even after most careful examination are able to detect nodules only in a very small proportion of such sufferers. Extremists have, however, recently asserted that this is because sufficient patience and practice have not been given to the examination.

2. Nodules are frequently found in patients who make no complaint of rheumatism, whatever.

3. The findings of certain early authorities on the pathology of these nodules have not been generally confirmed.

* Received for publication May 27, 1941

4 Increasing doubt has been expressed about deep, painful massage being able to rub away fibrous tissue (On general grounds we might expect this violent trauma to increase the fibrous tissue)

5 The etiology is purely speculative

In short, the commonly accepted theory of fibrositis is a top-heavy superstructure erected on some very simple clinical observations, namely that in certain patients with non-arthritic "rheumatism," thickenings and nodules can be felt on palpation in or near the region complained of, and these may be very tender to touch and pressure, also, in certain instances, sections of tissue taken from the nodule or thickening show minor pathological changes of an indeterminate and non-consistent nature

Psychoneurotic Rheumatism This ungainly term stands for the idea that upsets in the emotions may bring about upsets in the body including subjective symptoms of pain, stiffness and limitation of movement which appear on medical certificates under such names as muscular rheumatism, fibrositis, sciatica, neuritis, lumbago, pleurodynia, etc It is recognized that the inclusive term of "non-arthritic rheumatism," as well as its localizing names, covers a hodge podge of illnesses entirely diverse in etiology and nature, but it is considered that a considerable proportion—perhaps 40–60 per cent of patients who have been for two months or more on the sick list—can be understood only in terms of a psychoneurotic concept That pain may be a symptom of hysteria has long been accepted, but due attention has not been given to the aches, pains and stiffness which may accompany chronic psychoneurotic anxiety states or psychotic depressions Moreover, recent evidence suggests that, in certain persons, upsets in the emotions may also bring about upsets in the physical body or soma, i.e., disturbance of the psyche (in the sense of the emotional self) antecedes and determines the nature of the disturbance in the neuro-endocrine system, which in turn brings about derangement in metabolism both general and local, leading to the formation of what many writers call "fibrositis"

In order to appreciate this point in practice, it is, however, necessary to supplement our routine physical examination with a psychological approach

MEDICAL EXAMINATION AND ITS MODERN SUPPLEMENT

Although the relevance of psychological factors to illness was recognized by physicians from earliest times, their importance and significance were forgotten during the nineteenth century as the mechanistic outlook began to dominate medicine The modern study of psychoneurotic illness has enabled these reactions to be formulated in a scientific way, and there is now evidence available which demonstrates that any system of medical thought which neglects environment in its psychological aspects is misleading in its theory and often unnecessarily futile in its practice

The basic medical examination of the teaching schools consists of instruction in (a) history-taking confined to an account of the procession in

time of somatic symptoms, (b) identification (diagnosis) of the faulty part or parts, (c) etiological investigation confined to those factors (physical, chemical or micro-organic) which an individual encounters with his *soma*. The range of observations elicited by this investigation, however, may be too narrow, and modern medical knowledge requires us to make a supplementary examination which includes

- (a) "Looking upon the man," i.e., consideration of the patient's face and manner

Some doctors seem very insensitive to this aspect of a patient. Facial expressions which give us a hint that the illness may have emerged from emotional reaction may be divided into two extreme groups—the anxious, and the detached. The anxious face may be described as strained, tired, worried or hunted, it is associated often with fine tremors of the outstretched fingers—which are detected readily against a background of newspaper print, with tachycardia or visceroptosis. At the other extreme, the detached face may be restful, placid, complacent, smiling, or "spiritual"—in short, pathologically free from anxiety. It is associated sometimes with marked thudding of the aorta in the epigastrium. Detachment of face and manner is sometimes called "*la belle indifférence*" and usually indicates that the disturbing emotions, and sometimes also the situation which provoked them, have become dissociated from the consciousness of the patient.

- (b) An etiological investigation which includes those factors which the individual encounters through his psycho-neuro-endocrine system, e.g., personal relationships, quarrels and bereavement, occupational problems, financial circumstances, and fears and knowledge of disease.
- (c) Extension of the history-taking backwards in time, to include the disturbances in the psyche which preceded the disturbances in the soma.

The patient who develops physical symptoms during the course of emotional reaction tends to date the onset of his illness to the time when the physical symptoms first appeared. His preceding disturbances may have been very definite and very severe and included depression, lack of interest, inability to concentrate, feelings of futility and unreality, etc., but an account of these is not usually volunteered spontaneously. The patient's consciousness is dominated by his bodily symptoms, and those preceding disturbances are suppressed. We must, therefore, direct our investigation to two points in time, not only to the date of onset of the bodily disturbance but also to the date of onset of the various psychological symptoms which preceded them and may still accompany them. Sometimes we find that there is a lightening or release of the psychological symptoms when the bodily symptoms appear. Psychologists describe this phenomenon by saying that the emotion has become *converted* into the bodily symptoms. When the conversion is complete, the patient's interest is concentrated almost entirely on his bodily symptoms, the treatment he has received, the number of doctors he has visited, and the possibilities of securing further varieties of treatment. It is not always easy to induce such a patient to talk about the difficulties which he has met in life because he repeatedly short-circuits the conversation back to his symptom, the treatments he has received, etc.

If we omit this supplementary examination, the true nature of many disorders including non-arthritic "rheumatism" cannot be established, and, as a result, treatment may be inappropriate. Recent researches and observa-

tions in psychosomatic medicine show very clearly the need for extending the scope of academic medical examination if action, i.e., treatment or prevention, is to correspond with reality

THE CONTRIBUTION OF A PSYCHOLOGICAL APPROACH TO ETIOLOGY

A The Etiology of Onset

When applying a simple psychological approach as a supplement to ordinary examination it is useful to arrange the findings as answers to these three questions of etiology of onset, viz (1) What kind of person was this before he developed pain, stiffness and limitation of movement? (2) Why did he develop these symptoms when he did, i.e., to what external events were they the response? (3) Why did he take these symptoms in the way he did? When we adopt this formula as a framework in which to arrange our observations, we often obtain answers such as the following

1 *Kind of Person* Many of the patients who develop non-arthritic rheumatism have fairly well defined psychological characteristics, e.g., they are unduly independent, excessively upright, have a high sense of duty, and are conscientious workers. In their own words, "They keep themselves to themselves." A psychiatrist would doubtless summarize these characteristics by the term "obsessional." Such patients are rigid, stiff or touchy people before they become ill, with the rigidity, stiffness and wincing responses of rheumatism, which from this point of view may be regarded as a manifest expression of their latent attitudes to life.

The previous medical history of patients with non-articular rheumatism also deserves a short comment. Many of them have on previous occasions suffered from psychoneurotic illnesses in the form of "breakdowns" or from psychosomatic illnesses—not only the ill-defined gastritides, but also the radiologically confirmed peptic ulcer, or the irrefutably recurring bronchitis. It is usual for nervous breakdowns, gastritis and peptic ulcers to occur earlier in the time sequence than rheumatism and bronchitis. The triad of peptic ulcer, rheumatism and bronchitis is one which crops up again and again in the medical history of middle aged "chronics."

2 *External Events* As the kind of person who develops these symptoms tends so often to keep himself to himself it is not always easy, especially in a single interview, to elicit the environmental factors or external events which precipitated deep-seated emotional reaction. However, after ordinary examination has been made it is useful and often helpful to sit back and slowly say "It sometimes happens that symptoms such as yours (and here the examiner details them), begin at a time when a person is under some mental stress, or distress, or strain, or upset, or indecision. (Then after a pause) Does this happen to apply to you?" The question should not be pressed, but often the patient immediately and spontaneously tells the Doctor his difficulties, or he may do so at a second interview after a period of rumina-

tion By means of this question, addressed meditatively to the mid-air, so to speak, it is often possible to discover from a patient how shortly before the onset of his rheumatism he met with some very disturbing event, e.g., the loss of a beloved person, of money, of career, or difficulties in his occupation Thereafter the following sequence of happenings may be traced The frustrating events provoke emotional reactions, especially those of grief and rage as well as of guilt, and these are associated with feelings of soreness and hurt This inward (or mental) pain and anguish is in turn displaced into outward (or physical) pain and anguish The latter, indeed, is often the measure of the intensity of the former With the emergence of the bodily suffering there is usually some lightening of the mental suffering, and the attention of the patient becomes focused on his rheumatism and thus released from his life's problems and inner tensions

3 *The Manner of the "Rheumatism"* Having noted how physical pain may be the expression of mental pain, and how physical stiffness and limitation of movement may be the outward and visible signs of a corresponding attitude to life, we are now faced with the following question Why do particular persons select particular sites of the body for these "rheumatic" manifestations? (I have discussed this problem fairly fully elsewhere) It may be said here that, in addition to considering previous injury or disease which may render a site "inferior," account must also be taken of the symbolism of the symptoms For example, pain and stiffness in the posterior midline, either at the back of the neck, between the scapulae or in the lumbar regions, often symbolize inward feeling of resistance, obstinacy and resentment Again, pains in the arms and legs associated with numbness, tingling, deadness and losses of power, may symbolize repressed desires to attack (aggression) Thus it is sometimes useful to ask certain patients with "sciatica"—"Whom or what do you want to kick?" Nor must we forget the symbolism of the left side, which in the human psyche is the side of the body related to sinister feelings of loss, evil or magic Only when we begin to take note of whether a unilateral pain is on the left side or the right do we begin to learn how dominant are left-sided symptoms in non-arthritis rheumatism In this connection mention may be made of the typical (but seldom realized for what it is) "left shoulder neuritis" which so often is a *neuritis of deprivation*, not, however, of vitamins, but of a married partner or other dearly beloved person or object It is common in widows and widowers, and in married persons who are estranged or separated, whether through disagreement, by long illness, or by distance of land and sea But if these matters are not sought out they will not be volunteered

B The Etiology of Recovery

When we have discovered the relevance of the psychological approach to the etiology of onset, we can then begin to take note of its value as an aid to understanding the etiology of natural recovery, i.e., why do patients,

even in the absence of treatment, begin to get better when they do? When we inquire into such recoveries after a long period of incapacity, we find that many of these patients have encountered some new environmental factors which lessened the adverse pressure of circumstance, made life bearable again, and brought about a slackening of resentment. The process indeed may be likened to that of the child who won't play, who decides to join in the game again.

C The Etiology of Prevalence

The psychological approach may also provide a contribution towards our understanding of the geographical distribution of non-arthritic rheumatism which, it is now accepted, cannot be related to climatic influences alone. For example, it is established that non-arthritic rheumatism is unusually prevalent in the northeastern districts of Scotland round Aberdeen. This area may be regarded as fairly cold, but not unduly wet. It has, however, other features which may also be highly relevant. Its inhabitants are classical examples, whether by inheritance or Calvinistic culture, of the "obsessional" type already described which (as investigation of individual patients suggests) is especially liable to develop non-arthritic "rheumatism."

The prevalence of rheumatism over a period of years may also be related to the increase or diminution of what may be called the pressure of noxious psychological communal environment. For example, in Scotland during recent years, at a time when unemployment was increasing and people were losing the vision of life, incapacitating sickness rose very considerably, especially in the chronic groups. The interesting feature of this rise was that it was made up entirely of those diseases which are now being recognized as psychoneurotic or psychosomatic. Leaders in the rise were peptic ulcer, gastritis, nervous debility, pleurodynia and rheumatism (Halliday, 1938).

It must be admitted that medical men who are unaccustomed to applying a psychological approach to their "cases of fibrositis" will assuredly consider this newer (and older) way of looking at things as very curious and quaint, having nothing to do with the case. Unfortunately, so often it has practically everything to do with the case. If any such can overcome their resistance, cease "thinking" (in the Hunterian sense) and condescend to "try" (i.e., supplement the usual physical examination by inquiries along the lines indicated above), they will find how often this method of medical examination not only "fits" but also "works."

PSYCHONEUROTIC RHEUMATISM IN PRACTICE

In practice psychoneurotic rheumatism takes many forms, but I have found the following a useful classification.

1 *Hysterical Pains* Among the insured patients whom I see in my capacity of medical referee, such pains are comparatively rare, except in persons engaged in occupations which expose the individual to excessive bodily danger. This applies particularly to workers at depths (typically

underground miners), and workers at heights (typically steel erectors, slaters, window cleaners and steeplejacks) Other common occupations dangerous in this respect are those concerned with the manufacture of explosives, as well as those sports and pastimes, e g, football, which involve a high degree of bodily risk There is known to be a close relationship between hysteria and threats to bodily preservation This has recently been emphasized by Kretschmer who notes how often hysteria "develops out of a gradually progressive anxiety for one's safety" Unfortunately, many persons with "hysteria simulating rheumatism" are admitted all too readily to centers for physiotherapy, with consequent fixation of the symptoms There are many reasons for this, e g, (a) the still lingering superstition that hysteria is rare in men, (b) the failure to take note if the person's occupation is a dangerous one, (c) the omission to examine for marked thumping of the aorta in the epigastrium—a sign not necessarily diagnostic, but suggestive when present

2 *Pains, Aches, Stiffness and Limitation of Movement as Episodes in Chronic Psychoneurotic Anxiety States and in Psychotic Depressions* These are very common In my experience as a medical referee of the insured persons, about one-third of these patients who are labelled by their doctors with terms indicative of non-arthritis rheumatism, and who have been on the sick list for several months, readily fall into this category A full account of this inquiry is given elsewhere (1937) The reason for the non-recognition of the true nature of these disorders is the failure of academic medicine to indicate the need for a simple psychological approach as a supplement to ordinary physical examination In the absence of observations made by this technic of approach much incapacity preventable at the beginning becomes permanent and fixed

3 *Fibrositis* This note unfortunately must be confined to a personal confession I happen to be one of those who often fail to discover by palpation fibrositic nodules vouched for by other medical men, although I must admit that sometimes, in the presence of an enthusiastic demonstrator, I am led to "imagine" I can feel them This does not mean that I am unacquainted with nodules I discover them from time to time, but, again, unfortunately, I seem to find them as frequently in persons who have no complaint of rheumatism as in those who have Because of this personal inability, I have hesitated to make a serial inquiry about the prevalence of fibrositis in any group of persons labelled "non-arthritis rheumatism" by their medical practitioners The term fibrositis, in virtue of its implied idea of inflammation, has always seemed to me a misleading one in clinical medicine, although of value to a pathologist Fibrositis in the sense of inflammation of fibrous tissue (as, for instance, after sore throat) is understandable and in such instances my dominant clinical impression is that the patient is physically ill But in the so-called "true rheumatic fibrositis" I am impressed far more by the patient's behavior and attitude, inasmuch as it conveys the feeling that I am confronting a strained, unhappy distraught

individual and that the fibrositis is a purely local manifestation in a process of reaction of the person as a whole. This clinical intuition is difficult to put over in words, but the phrase "looking upon the man" seems to summarize it in a communicable form. In other words, to be misled by "itis" in the word fibrositis and to concentrate on the local phenomenon of nodule or induration tends to make us miss the value of the concept of psychosomatic disturbance, or, if we like to use the term "disease," of psycho-neuro-endocrine disease.

Four Cases of "Fibrositis"

I have selected four patients to illustrate in outline the practical issues raised in the paper.

CASE REPORTS

Case 1 Following the publication of my preliminary report (1935) on psychological factors in relation to rheumatism, I received a letter from an elderly surgeon in which he told me that he had at last come to understand the true nature of the serious "rheumatism" from which he had suffered some years before. He gave me permission to quote "his case."

Until the age of 60 he "had never known what rheumatism was," but at this time he became ill with severe pain in the left shoulder, upper left arm and left costal areas. He attended various specialists, who agreed that "the case was one of severe and extensive fibrositis." He was persuaded to go to a Spa, but was so crippled he had to be lifted in and out of the bath. Various forms of physiotherapy were given with no improvement. Finally his counsellors decided that the only thing to do was to "break down" the fibrous adhesions under an anesthetic. The patient, however, refused this procedure and returned home. After a further month of agony "quite surprisingly I got better within a few days."

As regards the etiology of onset, particulars of the "kind of person" he was are scanty. He was attached to the staff hospital, and on reaching the age of 60, the usual retiring age, he expected to be retained "in view of his services." To his shock and surprise he was informed that he was to be retired. This hurt him very much—"I lived for my work." He had little to do, and fell into a state of boredom, depression and resentment. During this unhappy emotional phase his rheumatism emerged. As regards the etiology of recovery, about a month after his return from the Spa he received unexpectedly "an offer of an appointment as surgeon in a neighboring hospital. Life became worth living again. I got better within a few days."

Comment This patient presents an example of left-sided symbolism, the sinister event being the loss of the loved object, in this case his work and reputation as a surgeon. Was he "a case" of fibrositis or of psycho-neuro-endocrine rheumatism? We may accept the presence of "true fibrositis"—leading authorities had confirmed it. However, it is evident that the psychoneurotic concept cannot be omitted in any understanding of the phenomena. A better all-in descriptive term would be psychosomatic non-arthritic rheumatism, or alternatively psycho-neuro-endocrine disorder with fibrositis as a dominant physical symptom.

This patient appended as a postscript to his letter the following: "I happened to read your articles on rheumatism when I was on vacation as a ship's surgeon. At

that time I had in the sick bay a fireman who had taken ill some days before with severe pain in the left neck and lumbar region which I ascribed to fibrositis. Armed with a new viewpoint I visited him and tried to persuade him to talk about the kind of thing you mentioned. Sure enough, I caught a fish! I found that at the last port of call he had been fined and logged for drunkenness and that the chief officer had told him that the Company would dispense with his services when he reached Liverpool. The man's previous record had been good, but he had evidently received a letter from his wife which worried him and had set him on a drunken bout. Anyhow, after his interview with the Chief Officer he became oppressed with a feeling of hopelessness and resentment. At times he said 'he did not know where he was,' and he pictured himself not being able to secure a job again. Some days later, the rheumatism appeared. I thought I would try an experiment in treatment in the light of this information, and I explained my idea to the chief officer who was interested and who agreed to inform the man that his sins were forgiven and his misdemeanor would be officially erased. Next day, the pains had almost cleared, and on the following he resumed his duty. It seemed to me that if I had not made the further inquiries which I did, the man would probably have been on the sick list until we reached Liverpool, and after that would probably have haunted the hospitals receiving many courses of massage."

Case 2 A medical practitioner told me the following: "I had a patient, a childless widow of 38 years, who after the death of her husband eight years previously developed a neuritis of the left arm which lasted for nearly two years. Rather than return to her family she decided to take an apartment house and to earn her own livelihood. She obtained a secretarial position in a warehouse, and remained cheerful at work and had a fairly extensive social life including attending church and bridge parties. Six months ago she consulted me because of severe pains in the lumbar region. I could make out nothing definite, but she seemed in considerable bodily distress. I tried to find out from her if she had any difficult emotional experiences in her life lately, but she denied this, and admitted only to some overwork at the office. I accordingly sent her to see a physician at one of the hospitals, and he diagnosed widespread fibrositis and recommended a course of physical treatment including massage. However, yesterday, to my complete astonishment (I should not have thought it of this woman) I learned from private sources that for several years she had been associating with a married man who was rather a bad lot. It appeared that shortly before she reported sick he had got into financial difficulties and had begun to blackmail the patient for money threatening her that if she did not give it to him he would inform her relatives that she was his mistress."

Comment I have included this patient to illustrate the difficulty of discovering relevant etiological factors in persons who keep themselves to themselves. The "lumbago" symbolizes resentment, resistance, threats to pride and independence and other related ideas. The term "fibrositis," granted that nodules were present, again seems inadequate and even misleading.

Case 3 This was a married man of 38 years who in March reported to his Insurance Practitioner with a complaint of severe pain between the scapulae and of pain and stiffness in the left lumbar region. The patient explained to the doctor that on the previous day he had been thoroughly soaked and together they accepted the etiology of the "rheumatism" to be a "chill." The doctor diagnosed fibrositis, prescribed aspirins and some liniment. The patient was still on the sick list when I saw him in June three months later. He looked tired and anxious and was inclined to be resentful because he had been summoned before a medical referee. I was not able to

satisfy myself about the presence of nodules I then investigated the details of his soaking and elicited the following

He was a hard-working conscientious man anxious to do the best for his four children. Eight years previously he had had a perforating gastric ulcer, but since that time he had been well, apart from a severe and prolonged attack of bronchitis two years previously. He had had no previous rheumatism apart from occasional "twinges." As regards employment, apart from his two periods on the sick list he had been continuously at work, but in January, through no fault of his own, he had fallen out of employment. With this he became very depressed and for the first time his thoughts turned to the political system which allowed such things to happen to respectable, decent working men. During this mood of depression he was told by the Labor Employment Bureau that if he visited a firm in a town eight miles distant, he would probably secure a job. He was by now in debt, and he had no money to pay his bus fares. Accordingly, he decided to walk, but a lashing rainstorm came on, and as he plodded through it his temper rose. In his own words "he was so upset in his feelings that he decided to refuse the job even if it was a good one," and in actual fact this is what he did. He returned home in the pouring rain and when he got there, he refused to speak to his wife and lay down in his bed. When he tried to get up next morning he found he was unable to do so because of his pains.

As he related this story, he showed considerable emotion and shed some tears. I told him how often pain such as his came on during a time of deep-seated mental stress. He seemed to see the point, and admitted that such things were possible. We talked matters over, and although I retained him on the sick list, I received a letter from him the following week telling me that he had now secured some work and was "almost well."

Comment This man may or may not have had fibrositis. He was certainly ill. Note the previous history of peptic ulcer and bronchitis. The soaking may have been a factor in the etiology of onset—it is not possible to say, but so often one finds that patients "rationalize" these physical encounters (example, chill, heat, cold, bad air, soaking, etc.), and further inquiries reveal that the dominating etiological factors were psychological.

Case 4 This was a married woman aged 30, a bus conductress, who on July 18 developed pain, stiffness and swelling of the left great toe so severe that she had to be carried from her work and put to bed. There she remained and about two weeks later she developed pains in the left shoulder and left neck as well as pains and swelling in the region of the left sternoclavicular joint. She remained in bed under the care of her insurance practitioner until September 20. Eight days later she was referred to the out-patient department of a hospital where, after roentgen-ray examination and elimination of gonorrhea, a diagnosis of periarthritides was made. She was given courses of massage, heat and electricity, and I did not see her until November 4, when my clinical notes read as follows: "Stiffness of both joints of left great toe but no definite swelling. Definite thickening—almost as if fluctuant—but no tenderness of left sternoclavicular joint, also slight thickenings over the joints of the second and third left sternocostal junctions." However, two other points impressed me. Firstly, her manner which was placid, smiling and composed. Secondly, it was extraordinary to find these physical signs confined entirely to the left side. Together these points suggested the possibility that psycho-neuro-endocrine mechanism must have played a prominent part in inducing her illness.

Her story was as follows. She was married in 1928, and a child was born in 1930. That year also her husband left for America. At first he was able to send her money

but this lasted only a short time. Rather than depend on her parents she decided to take up employment as a bus conductress. She was able to do this and live with her parents who looked after the child. Although her husband was unable to support her, he continued to write regularly, but in January of the present year he ceased writing, and as the months passed she thought he had deserted her. Also in January she was transferred to another town and had to live in lodgings. This not only reduced her income but also prevented her from seeing her child. She became depressed and sleepless. Her father was continually writing her to get into touch with the proper authorities with a view to tracing the whereabouts of her husband but she was afraid to do this in case her worst fears might be confirmed. On July 15 her landlady went on holiday and she transferred to new lodgings. She felt totally alone and abandoned and could see no way out for the future. Three days later she collapsed while on duty with severe pain in the left great toe.

It is noteworthy that she actually did hear from her husband on October 20, and he stated that he had at last secured a job and was looking forward to having her out beside him before long. According to her statement this letter made her feel better and since then her symptoms had improved somewhat. As the woman related her symptoms she broke down and after this we had a talk about the meaning of her illness and where the course of her life lay. She willingly accepted the sequence of events in relation to her symptoms. I asked her to come back three days later. She had lost that smiling detached facies and was somewhat anxious looking. Moreover, the swellings had entirely disappeared. Eighteen months later I learned from her doctor that following my two interviews she had resumed work and had never been on the sick list since.

Comment. The term periarthrititis is totally inadequate as a summary of this patient's illness and as a guide to action. The psychological approach contributed definite findings regarding the etiology of onset in respect to (a) the kind of person, (b) the external events, (c) left-sided symptoms. (I must admit, however, that I have no idea why the great toe and sternoclavicular joints were chosen.) It also contributed towards an understanding of the etiology of recovery—the letter from her husband, the telling of her story, innocence replaced by insight, and the return of the will to work for her child. This problem, the etiology of recovery—why does a person get better when he does?—has been, in the past, far too much neglected.

These examples must not be regarded as isolated ones. Any medical man will find similar cases in his every day practice if he cares to look for them. Any specialist in rheumatism who neglects the concepts contained in the term "psychoneurotic rheumatism" may be compared to a motor mechanic who is content to repair a hole in the tire with the very newest of patches and solutions, but who considers it beneath his notice to search for the nail to which the lesion was secondary. And the nail, like the underlying psycho-neuro-endocrine disturbance, tends to bring about recurrences of "the condition" either at its original site or elsewhere.

CONCLUSION

How do we differentiate between "true fibrositis" and "psychoneurotic rheumatism"? At present the answer is, by working more and talking less. In other words, the differentiation depends on the nature of the observations

we make rather than on the views we hold. In practice this means the following

1 Examine the patient honestly and do not detect abnormalities which are not there. If nodules and indurations are not present do not, on any "theory of fibrositis," deduce their presence. If nodules are demonstrable, remember that the etiology is not known in any scientific sense.

2 Whether nodules are present or not, always include a *psychological approach* as a supplement to routine medical examination. When they are absent, this approach may point the way to a diagnosis of hysteria, chronic anxiety state or psychotic depression. If nodules are present, a supplementary examination may indicate very clearly how the rheumatism emerged during a period of intense emotional stress, and, as we come to realize how often "fibrositis is cured" when emotional stress is relieved, any observations we may make on the life situation of the patient may provide us with guidance for action (treatment) much more valuable than routine courses of physiotherapy which take no cognizance of important etiological factors.

REFERENCES

- HALLIDAY, JAMES L. Psychological factors in rheumatism, a preliminary study, *Brit Med Jr*, 1937, 1, 213 and 264. The psychological approach to rheumatism, *Proc Roy Soc Med*, 1938, xxxi, 167. The rising incidence of psycho-somatic illness, *Brit Med Jr*, 1938, 11, 11. *Proc Roy Soc Med*, 1937, 1938, xxi, 167. Report on the recent incidents of psycho-somatic illness, 1938.
- KRETSCHMER *Brit Med Jr*, 1937, 11, 574.

SCHIZOPHRENIA; A NEUROBIOLOGIC APPROACH*

By ARTHUR O HECKER, F A C P , *Indianhead Gap, Pennsylvania*

THE approach to an understanding of the mechanisms responsible for mental illness has definitely entered a new phase, one characterized by attempted synthesis of data acquired through distinctly separate methods of investigation. This is basically a neurobiological methodology which utilizes data ascertained by the various individual methodologies which are applied to the study of the development, form, and function of the nervous system. This approach attempts to bring psychological studies with their multitudinous ramifications to a physiological level, i.e., it is an effort toward the interpretation of psychological data in the terms of neuronic development and function. It attempts, by outlawing the dichotomy of psyche and soma, to view psychology and the development and physiology of the nervous system as part and parcel of the same thing, the mind being defined as the objective and subjective expression of the biophysical function of the cellular units of the nervous system.

Such a methodology picks up the loose ends of phylogenetic, embryologic, anatomic, biophysical, biochemical, pathologic, clinical, and comparative and human psychological studies of the nervous system and ties them into a unitary methodology which represents not the partial perspective of separate methods of investigation, with their conclusions based on incomplete data, but a total perspective or comprehensive schema.

Even the most superficial use of this method of investigation makes apparent certain principles of nervous function which have been either overlooked or, if discovered, not utilized in the synthesis of data which have gone into the formulation of etiologic doctrines in the past. By bringing phylogenetic studies and studies of comparative behavior into the scheme of investigation we feel that we have been able to draw certain conclusions which may serve to re-orient the investigative approach to and the interpretation of the neurodynamics behind so-called functional mental illness.

Schizophrenia probably represents the major problem of psychiatry. This is not only because it is so economically and socially important, but because a clearer understanding of the mechanisms behind the schizophrenic process can unquestionably throw considerable light on other psychiatric problems and lead to more concrete knowledge of neuropathology. It is for this reason that we are attempting to present here a neurobiological or comprehensive interpretation of schizophrenia.

For the most part, the nervous system has been studied without consideration for its phylogenetic status. Likewise psychological studies, while frequently taking into consideration phylogenetic processes, have not been fully

* Received for publication November 30, 1939

cognizant of the importance of determining man's phylogenetic status other than to place him at the top of the phylogenetic scale. This is too static an interpretation. Man can not be considered as phylogenetically mature, as we will see. This is a most important consideration in any study of the function of the nervous system. By considering man as a phylogenetically immature creature, a being in transition, the synthesis of investigative data is simplified, many of the apparent antinomies arising from separate investigative methodologies are solved, and a better perspective of neural mechanisms and the behavior that results is obtained.

PHYLOGENETIC BACKGROUND

All living organisms, from the simplest protozoa to the highest metazoa, expend their vital energies toward the attainment of two specific goals, i.e., self and species maintenance. These goals themselves are served by three universal biologic impulses—the urge to seek sustenance, the urge for protection from inimical environmental influences, and the urge to reproduce the species in kind. To these impulses we give the terms hunger, self-protectiveness, and love. Intangible as these things may seem, they are, nevertheless, as real as life itself, and even the most superficial survey of phylogenetic development forces us to accept, as a scientific fact, that these are the biologic constants which determine behavior throughout the phylogenetic scale from ameba to man.

In protozoa, protoplasmic irritability serves to adjust the organism to its environment and to adjust the internal economy of the organisms so that these ends are best served. In metazoa, because of cellular specialization for division of labor, the nervous system is developed for the specific purpose of maintaining the internal and external adjustment of the organism in its struggle for species and self-maintenance. Thus, it is at once apparent that, from the beginning, behavior and the structure and function of the nervous system are inseparable, the one the manifestation of the other. The definition of the word "mind" is then limited to the sum total of the function of the nervous system. It is also apparent that all organismal behavior, as well as the structure and function of the nervous system, is determined primarily by the two essential biologic goals of all living organisms in response to the impulses of hunger, self-protectiveness, and love, and that these premises must serve as the basis for all interpretations of behavior or nervous function.

Phylogenetic progress is an almost interminably slow series of events in which many factors operate continuously. In general it is characterized by an increased range of mobility associated with varying morphological adaptations to a successively more complicated environment to which the organism must react to secure, maintain, and reproduce life. With the evolution of a new species of life eventualities arise which require more complicated mechanisms and more complicated behavior patterns for existence. This

necessitates a concomitant increase in the functional and structural form of the nervous system. However, before satisfactory behavior patterns are well integrated and stabilized a long period of experimentation with the environment, as well as adjustment of the internal milieu of the organism to these experiments, is necessary. Species maturity is measured by the stability and consolidarity of the species-specific engrams and their universality among individual members of the species. In terms of neurophysiology this may be expressed as the functional solidarity of the neuron chains.

Functionally and structurally the phylogenetic development of the nervous system follows a distinct pattern and results in a progressive encephalization of the centers of control. The "master" of the entire nervous system is always found to be in its most cephalad portion. Likewise, the newest phylogenetic acquisitions of the nervous system, and, therefore, the least stabilized and consolidated or integrated by species experience, lie cephalad. Furthermore, each older level of function (phylogenetically inherited) is represented in each successive cephalad level so that it may be subject to modifications of function according to the environmental exigencies of the new species. This is essential for maintaining the internal milieu of the organism in satisfactory adjustment to the environmental contingencies with which the organism is faced.*

This means that each new species must pass through a period of transition characterized by two contiguous processes. New engrams must be worked out by experimentation with the environment. At the same time the newer nervous centers must assume control and dominance of older phylogenetic engrams. During this period of transition, the organism's behavior reflects this struggle between these two forces for dominance of the organism's behavior, i.e., reflects the struggle between newly formed engrams which are in the process of integration and old well consolidated phylogenetically inherited engrams. We find then that behavior during this transition period is unstable and varying in its manifestations, that it is, in fact, a compromise between two neural mechanisms, one well consolidated, the other in the process of being consolidated. Species maturity is reached only when the newer engrams attain complete dominance of older neural mechanisms.

In succession the midbrain, the thalamus, the corpus striatum, and finally the neopallium are developed with each in turn acquiring the "greatest compass of the control of behavior." With the acquisition of a highly specialized premotor and parietal cortex we come to man in whom we find the highest representation of the phylogenetic development of the nervous system: a nervous system in which there are "vague memories" of those centuries when the world was in its childhood."

* This statement leads to the conclusion that in vertebrates there is no actual division of the nervous system into the cortico-spinal and autonomic systems, a fact that is well substantiated by recent researches. These two systems, heretofore regarded as separate, are correlated at every level of impulse integration and can not be considered distinct in any real sense. Phylogenetic studies would point to no other conclusion, and it is interesting to note how many errors could be avoided in theorizing on human physiologic processes if phylogenetic studies were included in the formation of these theories.

Man's development is characterized by a gradual loss of effective defensive and offensive morphological mechanisms for combating inimical environmental influences and a concomitant gradual increase in inventiveness. In its broadest sense we speak of this latter as intelligence. In its strictest sense it is the ability to form concepts which adjust the organism satisfactorily to its environment. Structurally, this ability to form concepts has been shown to be associated with the development of the human premotor cortex, that part of the nervous system designed as the great association areas where through synaptic neurononic associations, by cellular polarization (Kappers), uniquely human behavior is initiated. Many recent experiments definitely place the seat of conceptual ideation in this region of the nervous system. Therefore, from what we know of phylogenetic development and comparative behavior studies, it is apparent that intelligence or, as we prefer, conceptual ideation is man's biologic mechanism for use in his struggle for species and self-maintenance in response to the urges of hunger, self-protectiveness, and love, i.e., the mechanism through which he adjusts himself to the environmental circumstances of his life.

We find, however, that in man's immediate phylogenetic predecessors the struggle for species and self-maintenance is essentially an individualistic struggle in which the weak and the unfit are rapidly eliminated. Individual strength is the ideal, weakness is synonymous with annihilation. Mutual assistance among members of a species in the struggle for existence is found on only the most primitive scales when observed at all. These forms of life, those that survive, are morphologically adapted for success in an individualistic struggle with their environment, and their behavior patterns or engrams are so designed. In man the situation is reversed, for man, even when endowed with a high degree of intelligence, is no match for the destructive forces of his environment as an individual. Gregariousness became mandatory for man as he lost his morphological defenses against natural enemies.

Gregariousness is man's primary species-specific behavior engram. If we study the history of the human race as far back as we can go with scientific theorizing we find that this was probably the first specifically human engram to be developed and is today the best integrated and consolidated of man's species-specific engrams. How well consolidated it is we will see later. All other strictly human behavior engrams and neural mechanisms have this as the pattern or ground-structure to which they must conform. Now, for this to be a biologically effective mechanism it must be supplemented by other behavior patterns which conform to its essential form. A communal type of existence, just as a multicellular type of existence, presupposes some agency which will maintain harmony of function. Out of this need developed moral obligation, the keystone, in a biological sense of effective communal life. The moral obligation of which we speak is not limited to the popular conception of the term "morals," but refers to that obligation each individual living in a communal state must assume toward

others for the welfare of the whole. To quote Bergson who summarizes this well. "It is society that draws up for the individual the programme of his daily routine. It is impossible to live a family life, follow a profession, attend to the thousand and one cares of the day, do one's shopping, go for a stroll, or even stay at home without obeying rules and submitting to obligations. Every instant we have to choose, and we naturally (*due to species-specific engrams—Author*) decide what is in keeping with the rule. We are hardly conscious of this, there is no effort. In the ordinary way we conform to our obligations rather than think of them. The members of a civic community hold together like the cells of an organism. Habit (*species-specific behavior engrams—Author*), served by intelligence and imagination, introduces among them a discipline resembling in the interdependence it establishes between individuals, the unity of an organism of anastomotic cells." And just as the nervous system is the cohesive factor in a group of anastomotic cells, moral obligation is the cohesive factor in communal existence. Moral obligation, in this sense, is the means through which a gregarious or communal type of existence is made possible, and thus is the means by which human life for the individual and the species is maintained. It is man's second species specific behavior engram.

It is now to be noted that these two behavior engrams or patterns have become "unconscious" functions, functions which have become so well integrated through species necessity and experience as to be considered "instinctive." If one considers species-specific instincts as unconscious reactions or drives found universally among members of a species, then we can consider gregariousness and moral obligation as man's species-specific instincts. Because they are species-specific and develop with the acquisition of a highly specialized premotor cortex their master neuronic mechanism must be represented in this area. But it is to be remembered that they are superimposed upon the individualistic instinct-engrams which man has inherited from his immediate phylogenetic predecessors. Thus, if the laws of phylogenetics hold for man, and there is no scientific reason to theorize to the contrary, then the species-specific instincts of man must eventually assume complete dominance of these phylogenetically older individualistic instincts and modify them to conform to the newer scheme of living if man is to be considered phylogenetically mature. In terms of neurophysiology, the neuronic chains for these instincts must completely regulate and modify older and lower neuronic chains. We can only conclude from phylogenetic studies that these instincts are manifestations of neuronic patterns which are as much predetermined for the individual as are the cellular patterns of the heart or liver, patterns which have been consolidated by (phylogenetic and species) experience.

It becomes apparent at once that this dominance has not been effected.

Man's behavior over the period of its recorded history, and we may presume before this, reflects a struggle toward this dominance which has never been quite achieved. Man's behavior is characterized by an endless struggle

toward intellectually ideal behavior based upon the laws of moral obligation, but is marked by that ebb and flow characteristic of experiment, is unstable and unpredictable, is fluctuant in its manifestations, is a never ending response to new and varied concept formation, and when broken down in analysis consists of an eternal conflict, both for the individual and the race or any of its component subdivisions, between individualistic animal urges and the urges of moral obligation and the intellectual concepts built around the concept or species-specific instinct of moral obligation. In the individual we daily see in every phase of behavior that this conflict is manifest, and in general we may discern it by the conflict of political, religious, and social ideologies for a "place in the sun." Man's behavior reflects a period of phylogenetic transition, a period during which new phylogenetic neural acquisitions (in this instance the human premotor cortex) are adjusting a new species internally and externally to its environment in an attempt to insure most efficiently species and self-maintenance. It is a period during which we would expect behavior to be "experimental," and we find daily evidence that it is. In terms of neurophysiology we find that man's behavior reflects a struggle for dominance of the neural mechanisms of the premotor cortex in its formulative stage over older phylogenetic centers with engrams which are well consolidated and integrated. It is in popular terms a struggle between human intelligence and animal instinct for dominance of behavior.

Therefore, from phylogenetic studies of neural development and comparative behavior we conclude that man is a being in transition, that his behavior reflects a conflict with varying compromises between his species-specific instincts of gregariousness and moral obligation, and the concepts built around these instincts, and the individualistic instincts he has inherited phylogenetically, and that this behavior reflects a functional attempt of an unstable and immature premotor cortex to dominate a stable and mature older nervous system in the struggle for self and species maintenance in response to the primal urges of hunger, self-protectiveness, and love. That this is of major importance in the development of the schizophrenic reaction we will attempt to elucidate.

DEVELOPMENTAL BACKGROUND

The development of the individual human fetus from conception to birth is essentially a rapid recapitulation of the phylogenetic development of the species. In the fetal nervous system the phylogenetically well integrated reflex and instinctive levels are established early. As an example, we find that the neuron chains over which nervous energy flows for maintenance of cardiac action are intact and functioning by the fourth month of fetal life. Development within the fetal nervous system proceeds in relationship to the phylogenetic age of the part and does not proceed at the same rate in all parts of the nervous system simultaneously. Although many of the lower levels are functionally integrated by the fourth or fifth month of fetal life,

in the frontal lobes of a six month fetus "lamination has not yet appeared and the cells are of a uniform undifferentiate type (neuroblasts) They are small round cells with a close and readily stainable reticulum, but quite devoid of processes, and they lie embedded in a matrix which, in hardened and stained sections, somewhat resembles the grain in marble In the eighth month embryo the neuroblasts are somewhat larger, the reticulum is less close and has less affinity for stain, but there are as yet no definite processes At this age signs of lamination are very clearly seen in the frontal region of the cortex In the motor area of the cortex of the eighth month embryo medium size pyramidal and also Betz cells are readily recognizable" ¹

At birth the structural development of the nervous system is far from complete The phylogenetically newest areas have not fully begun to take form, the cells of the frontal areas of the cortex being barely recognizable as nerve cells At birth the infant human being is, in truth, a "little animal," an organism without a frontal cortex Intelligence is only potential and neo-cortical association centers are not developed or integrated

From birth to physiological maturity, which we estimate biologically as full physical and sexual maturation,* the development of the human organism has as its goal "the functional integrity and dominance of the cerebral cortex" ² By two weeks progress is apparent, for the "cells of the frontal cortex have made a rapid advance in development and are recognizable as nerve cells A cell body is present, although the protoplasm of this differs from that of a mature cell, being very vacuolate and liable to break away A few years after birth these cells have assumed their mature character and are in possession of dendrites, axons, and gemmules" We find that the development of the premotor cortex and, thus, the development of intellectual capabilities (capacity for concept formation) is gradual and proceeds along a definite plan from the more simple faculties to the most complex It also reflects the steps of development of the human race from its evolution to its present state It is an hierarchy of neuronic associations within the general hierarchy of levels of the complete nervous system, and development proceeds from level to level in an orderly manner, just as it does in the nervous system as an organ Bolton³ substantiates this by showing that development of the cortex takes place from within outward and that at birth the outer stratum of the cortex is little more than half the depth of the stratum of the adult and exhibits an aggregation of embryonic cells

With the establishment of the need for a communal type of existence with its manifold problems of organization and integration, the need for a highly intricate method of communication between individuals is recognizable Speech developed in man's early period of evolution as a specifically

* That degree of maturity at which the individual is physically equipped for his struggle for species and self-maintenance in response to the urges of hunger, self-protectiveness, and sex, i. e. that degree of maturity which enables him to take his place as a mature member of a society

human mechanism and as a cortical function. Therefore, the development of the power of speech is in the infant the first objective manifestation of the functional integration of neuronc associations in the strictly human cortex.

The onset of speech is at about 19 months in boys and 18 months in girls. Karlin⁴ reports on the neurodynamics of the development of speech and is quoted here to illustrate graphically just how cortical control of older centers is effected and how, through cerebral association centers, older centers are tied into a new behavior pattern. It also shows how intricate are these new neuronc associations or engrams and that these, being specifically human, depend upon an intact neocortex. Karlin's discussion is summarized as follows. A normally developed cortex is essential for speech. The normal activity of the cerebral cortex is dependent upon the interaction of two processes: the sensory and the motor. Myelinization of fibers of the central nervous system proceeds in the following order: (1) the sensory, (2) the motor, and (3) the association fibers. Speech impressions are received in the cerebral cortex by all the senses: auditory, kinesthetic, tactual, visual, gustatory, and olfactory. For the normal development of speech, at least one of these senses, i.e., good hearing, is indispensable, especially in the early periods of childhood. The sphere of hearing in the temporal lobe of the full term newborn infant can be sharply distinguished by its marked myelinogeny in contradistinction to other temporal spheres, and from all evidence the auditory mechanism is well established at birth. The auditory word area is at the upper, sylvian, surface of the temporal lobe and in the adjacent posterior end of the first temporal convolution. The visual word area is the angular gyrus. The auditory word area is connected by association fibers with the motor speech area, Broca's area, located at the posterior end of the inferior frontal convolution and in the adjacent parts of the precentral convolution and of the insula. The visual area is linked with the motor area for writing, which has not been definitely placed. Myelinization of the motor tracts is not complete at birth. Even nine months after birth myelinization of the pyramidal tracts is not complete. At birth the fibers of the olivospinal tract have not even begun to myelinate. Since speech depends upon the functional maturity of both sensory and motor pathways, as well as of the association centers, it cannot begin until myelinization of all components is complete.

There is no peripheral organ or set of organs that has been set aside by nature for the peripheral production of speech. All the structures that are used for articulation have been serving and are serving purposes biologically more fundamental than speech. These are the functions of respiration, mastication, and deglutition.

It is readily apparent, then, that the first truly human neural mechanism to be developed is associated with the functional and structural maturation of areas of the neocortex, and in its development makes use of and modifies lower neuronc patterns. Also, "there is a universal unanimity of opinion

that speech is an index of the mental development of the individual Mental (intellectual) retardation has to be considered when a child of two and one-half or three years has shown no attempt at vocalization "

Following vocal expression the next step in cortical development is shown by the formulation of coherent sentences, a task which requires development of cortical association patterns involving all sensory components listed above and a complicated and intricate association and motor system This develops as the neocortex develops structurally

If we accept the appearance of speech as the first indication of the functional integration of the human neocortex, and, *ipso facto*, as the first indication of intellectual development we can trace the intellectual development of the individual from this stage onward as an expression of the gradual structural and functional maturation of the neocortex and will have established in the human premotor cortex a structural and functional basis for intellectual activity

It is generally agreed that the human brain is structurally mature at about six years of age, i e., that the numerical maturation of neurons is complete From this period until well into middle life development is represented only by a numerical increase in cellular processes (dendrites) and an increase in the number of neuronic associations The period from the time of the appearance of speech until about six years of age represents the period of structural development of the physical substrate of "conceptual ideation" From six years to physiologic maturity represents that period during which intellectual engrams and concepts of behavior are integrated and consolidated by precept and example, and during which the highest cortical centers are stimulated by experience and instruction toward the ability for thought synthesis, about which more will be presented later

It is during the formulative period of development, both from a behavior and neurological standpoint, for the two are inseparable, that factors of importance in the understanding of schizophrema develop

During this period the individual is not a "free" organism, but is under the guidance of his creators, his parents or their substitutes It is the period of protective education in the laws of human behavior on one hand, and a period of protective instruction in the mechanisms required for "free" existence in a communal adult society on the other Of the former we may refer to this phase of development as the inculcation, in the developing mind, through stimulation of neuronic associations by repetition and reiteration, of those idealistic concepts of behavior which have been passed through generations of human existence, modified and amended according to circumstance, and which reflect the experience of the race In other words, it is during this period that the individual learns the rules of behavior according to the religious, economic, and social ideals of his instructors and through painful and pleasant personal experience The "instructed" neuronic associations or behavior formed during this period are precepts, not concepts, i e., the stimuli and the neuronic associations they produce are "from the out-

side" and, if we may use the term, they are mechanical acquisitions. The ability for concept formation at this period is limited and immature and functions only in response to poignant stimuli of pleasure or pain. The biologic purpose of this training is, of course, to prepare for the successful socialization of the individual when he becomes "free."

The sensory-association-motor pathways formed through neuronically associations depend for their consolidarity upon one of two factors, both of which are continuously operating during the formulative period of development. On one hand we have stimuli constantly repeated and nervous energy flow over the same neuronically chains. On the other we have stimuli arising from a situation which is so poignant and intense that consolidation and integration of a high functional degree are effected immediately. Thus a child may be repeatedly told never to put its hand in a flame and eventually learn never to do so. Another child may never be so instructed, but once experiencing the pain of such an act, will never again perform it and will have a painful recollection of his experience to guide him through life. Therefore, experience and instruction (thus, total environment) play a major rôle in determining the behavior of an adult through the strength of the neuronically patterns they integrate during the formulative period and must be given major consideration in the interpretation of functional disturbances in the adult nervous system. We find that these are mechanical reactions which function more or less as closed circuits in which evaluation of circumstances does not enter into the response. Intensive religious training is an example of this. We may also explain it as an acceptance of facts without an evaluation of the total perspective of forces brought into synthesis in the formulation of behavior responses. It is the mechanism which underlies delusions in pathologic states, and is associated with a stage of neural development corresponding to that found in the formulative period of development. During this period "precept" behavior is the dominating neural mechanism in behavior although "concept" behavior is developing as the individual approaches physiologic maturity.

We may summarize the development of the human nervous system postpartum in another way, paraphrasing Jelliffe. In infancy both the level of intelligence and the products of intelligence (ideals) are weak and unorganized and the phylogenetically older levels are all powerful. The child lives in a phantasy world with its primitive pleasures. He has tantrums, or sulks, or cries when not satisfied, and laughs and gurgles when pleased. He mostly sleeps. Through pain and pleasure the intellectual or conscious level begins to learn about reality, and then through precept and example builds up its own nervous pathways as adaptations to the world. The unconscious phylogenetically older centers become guided by conscious experience, and still further controlled by the refinements of civilization (ideals) to such a degree that behavior is made comfortable to the mores in each particular situation, i.e., ideally becomes adaptive, successful, and pleasure giving. (Thus the older levels become sublimated and their forces become socially

creative and attain survival value, both individually, racially, and sociologically.)

Man becomes physiologically mature at puberty, i e., he is capable of mating and of reproducing his kind. The sexual urge in all lower forms of life reaches an intensity which demands satisfaction at the time of physiologic maturity. In the human organism this urge may be somewhat less intense at this physiologic period, but is nevertheless of sufficient intensity to arouse a mating instinct and to urge the individual to gratification. However, in a civilized state, through species experience and economic, social and other environmental circumstances contingent upon the instincts of gregariousness and moral obligation, there is a general agreement among individuals that the ideal age for mating is not at puberty but later in life, and that mating and reproduction must be consummated only according to certain sets of idealistically conceived laws. The necessities of communal existence on a civilized plane demand this, and in the developing individual nervous system, because of its general necessity, these "ideals" are inculcated through education, an education which consists of instruction by constantly repeated verbal stimuli, taboos, and stimuli associated with religious pageantry. Fundamentally it is an attempt, for the biologic purpose of species maintenance, to readjust a basic biologic urge and its physiologic counterparts to a pattern of behavior which is based not on an individualistic scheme but on the instincts of gregariousness and moral obligation by developing a dominance of neocortical neural mechanisms over phylogenetically older neural mechanisms and modifying these mechanisms to conform to the newer concepts. Non-technically it is an attempt by the intellect to accomplish a complete dominance of human ideals over animal instincts.

Obviously this attempted readjustment of the organism is not completely effected. If man were phylogenetically mature the dominance would be effected, i e., through the consolidation and integration of neocortical neuromic patterns and their functional dominance of older instinctive patterns these older patterns would be modified to conform to those patterns of behavior conceived, formulated and now only fairly well consolidated in the neocortex in response to the demands of a gregarious type of existence based upon moral obligation. But because the race is in an experimental stage of development the "ideal" type of behavior has not been fully determined, and neocortical dominance and modification can not be completely effected until a stable and universally specific engram is determined. Only then can lower neuromic patterns be completely modified. Therefore, when the individual reaches physiologic maturity two antagonistic forces are brought into play in the determination of his behavior and he is immediately thrown into a sexual conflict. On one hand he is subject to a basic biologic urge which demands gratification as an individual, and he has strongly integrated individualistic engrams, which he has inherited phylogenetically to accomplish this gratification. On the other hand, he has higher neuromic mechan-

isms, consolidated by species experience and throughout the formulative period of his life, which contradict these individualistic urges, but which are not well enough consolidated by species experience to dominate them completely and modify their function completely to conform to the "higher" demands. This results in the fact that his behavior, with regard to his sexual urges, is a compromise between these two antagonistic urges, and this sexual conflict with all its ramifications is a normal conflict contingent upon man's phylogenetic immaturity.

Much stress has been laid upon sexual conflicts in the pathogenesis of many functional mental disturbances as well as in schizophrenia, and it is for this reason we have indulged in the above delineation. We feel that this conflict is purely neurobiological and based upon man's immature phylogenetic status. However, this same state of conflict, which we have delineated for the reproductive urge, is also present and normal for the urges of hunger and self-protectiveness* and for the same reasons. Without going into detail, for we believe the implication is obvious, this is responsible for all of our political, financial, social, religious and ethical unrest as well as for the eternal conflict between individuals and nations. It represents a conflict between individualistic urges and moral obligation in which sometimes one and sometimes the other plays a dominant rôle in behavior. The point is that this conflict is "normal" and must be met in every situation which arises in our daily lives after we pass the age of physiologic maturity.

How are these conflicts met and how is behavior decided? This is the essential function of the highest centers of the neocortex, those centers concerned with "concept formation" or the centers for conceptual ideation. In every new situation with which man is faced in his daily life he is called upon to form a concept of behavior, through new cortical neuronc associations, which results in a compromise between animal instinct and human ideals. It is the function of the highest cortical centers to analyze the situation, to coordinate past experience with the probable results of the new concept on the future for the individual, and indirectly the race, and to effect a compromise between individualistic urges and moral obligation. In terms of neurodynamics every situation which is new for the individual and of sufficient intensity to require a modification of his past behavior or the formation of a new behaviorism requires the functional integration of new neuronc associations in the neocortex and the functional linkage of these with the parts of the lower nervous system to be called into play or modified in the given situation. Thus, the ability to form new concepts and compromises between animal instincts and human ideals is an indication of the functional integrity of the highest cortical centers. Whether or not the compromise favors the ideals based upon moral obligation, intelligence, or individualistic urges is an indication of the degree of neocortical de-

* Thus explaining Adler's urge to power

velopment The satisfactory compromise, from a biologic standpoint, is that which insures successful socialization of the individual *

GENETIC BACKGROUND

Although the burden of proof, except perhaps in the manic-depressive psychoses, indicates that so-called functional mental illnesses are not directly inherited as such, there are many indications that an "heredity factor" operates in the pathogenesis of such states Primary mental deficiency, because it exhibits a numerical deficiency of cortical neurons, as well as other directly inherited structural defects of the nervous system, may be excluded from this discussion as not pertinent We are concerned primarily with those states characterized by a structural sufficiency and a functional inadequacy The question resolves itself into whether or not the functional potential of cells of similar morphology differs in different individuals, and whether or not the degree of functional potential of the cells of the nervous system is influenced by heredity This is a question the answer to which must be found in clinical comparisons

From the fact that within certain families we find a more than coincidental number of individuals who exhibit functional disturbances of the nervous system and who often present a picture of neurosomatic inadequacy we can deduce that in these individuals there is a lowered potential for sustained neural activity It is also true that in a given trying situation these individuals react inadequately, whereas members of families free or comparatively free of nervous disorders are able to carry on without evidence of functional failure Hereditary functional inadequacy is noted with regard to other organs and systems, particularly with reference to the kidneys, heart and genital organs, and it does not seem illogical to assume that the functional potential of the cells of the nervous system is determined, in part at least, by heredity and that this must be given consideration in studying the pathogenesis of schizophrenia

PHYSIOLOGICAL BACKGROUND

The neuron is the genetic, structural, trophic, and functional unit of the nervous system It alone is concerned with the conduction of nervous impulses Therefore, the functional integrity of the neuron is essential to normal nervous mechanisms The functional integrity of nerve cells depends upon the continuous inter-reaction of the nucleus and cytoplasm to serve two purposes—to maintain the vitality of the cell and to carry on the transmission of neural energy over its circuit in response to the demands

*Let this be misinterpreted as a plea for communism or socialism, it is not, in fact, the opposite is true Communism is moral obligation carried to its idealistic pinnacle, as are the basic tenets of Christianity But man, as we have attempted to point out, is not a purely idealistic creature even if these doctrines to be practical, for they fail to take into account the physical and the social, besides the powerful but total subjugation as yet to be achieved in a matter of centuries or so, but longer

of the organism. These functions depend on the availability of metabolites and the functional ability of the neuron to transmute these metabolites into nervous energy. Nervous energy expenditure and repletion, in accord with the universal law of energy, is the ultimate problem of nervous physiology, and, in the ultimate analysis, all behavior from the most simple to the most complex depends upon the conversion of carbohydrate into nervous energy.

Obviously the more work a cell or group of cells is called upon to perform the greater will be the energy requirement and the metabolic rate. There are many ways of measuring this, such as the period of cellular activity which follows isolation of the cell from the source of combustive energy (oxygen), the degree of fatigue, and the duration of the period of energy restitution, measurements of oxygen consumption, etc. These studies indicate definitely that the highest metabolic requirements are found in the cells of the cortex. This is readily explainable if we analyze behavior patterns as they reflect the neuron level of function with which they are associated.

Reflex patterns of behavior involve nervous energy transmission over neuron circuits involving relatively few neurons, which are inherited by the individual, established early, phylogenetically consolidated, and well integrated by continuous and frequent use. The barriers to impulse transmission are minimal. Repeated use of any neuron circuit, once established, involves less and less energy as consolidation increases. This is well exemplified by the effort required to learn precepts and behavior patterns early in life which function with such facility once "learned" that conscious effort is not required later in life for energy flow over these circuits. The formation of concepts involves polarization of the cell body, extension of dendritic processes, and synaptic coordination of these processes with those of cells or cellular groups involved in the total reaction pattern. This is the most energy depleting process the nervous system is called upon to perform.

We may, therefore, postulate general levels of energy demands. From the lowest level of simple reflexes, requirements for function increase through the higher reflex levels, instinctive levels (phylogenetic mnemonic levels), human instinctive levels, patterns "learned" in the formulative period of development, concepts formed by the individual, to the level of active concept formation.

It follows that the function of the highest levels requires an adequate source of energy as well as the functional integrity of the cells of the neocortex involved in the formation of concepts to maintain normal human behavior.

We have outlined *above* certain backgrounds which we feel are essential to an understanding of the neuropathology behind the schizophrenic process. Each supplements the other and is a factor of importance, there being no one specific factor which is totally explanatory per se. The data presented may seem unrelated taken separately, but a study of the manifestations of schizophrenia, as well as those organic states which are capable of producing those

functional aberrations seen in schizophrenia, makes a correlation of these data possible

THE SCHIZOPHRENIC REACTION

The schizophrenic reaction may be initiated as a unique and relatively sudden change in a previously "normal" individual, it may evolve slowly from a mild or severe neurosis, or it may be superimposed as a culminating disaster upon an inadequate personality. However, its genesis, the primary universal manifestation from a behavior standpoint, is socialization failure. The patient stands apart from the majority to the extent that his behavior is noticeably "peculiar." The individual is no longer "one of us," but an abnormal personality unable to be successfully socialized. Many terms have been given to this earliest and universal manifestation of the reaction: personality distortion, personality isolation, personality disintegration, personality deterioration, unadaptable personality, and shut-in personality. The victims are called social misfits and they have been described as socially useless. They are frequently characterized as "extremely vulnerable to the hurts of the world" and are said to have withdrawn "from reality into phantasy." It is said that their behavior is due to "substitutive reactions," and that they are "dodging reality." The latter terms too often imply or are interpreted as indicating a willful reaction on the part of the patient, a conception with which we do not hold and which we feel is biologically unsound.

As the reaction progresses beyond this "incubation period" of socialization failure, evidence of a more pronounced psychologic or physiologic disturbance appears. The socialization failure becomes so marked that isolation from "normal" humanity often is required and behavior is overtly bizarre, the individual becomes useless to or detrimental to his community, occasionally a dangerously atavistic personality. He reacts to life as an individual and not as a member of a communal society. His obligations are only to himself. The psychiatrist finds that there is an illogical or incoherent association of ideas, thought deprivation, infantile cerebration, inconsistent thinking, faulty judgment, a loosening of association systems, emotional disturbances, attention difficulty, and a preoccupation with his own ideas, a withdrawal from the circumstances of the environment. The mental content is found to be dominated by false ideas or delusions, and insight is lacking. The patient is found to be unable to synthesize data into normal concepts of behavior, the association systems are disturbed. An analysis of the cerebration of the schizophrenic points to one universal finding which underlies all other manifestations of the process—the patient is unable to form those concepts which are required for socialization success, he has primarily a defect in the sphere of conceptual ideation, i.e., this level is excluded from the total reaction of the nervous system.

Lovin's analysis of the manifestations of schizophrenia bear out this

premise, i.e., the premise that schizophrenia results from a reaction pattern in which the highest cerebral centers (those concerned with "conceptual ideation") are non-functional. He concludes "In schizophrenia there is a loss of cerebral 'versatility' resulting in fewer and less complex concepts and in diminished capacity to differentiate concepts. There is a loss of autonomy of the cerebral parts . . . and an increased tendency to mass reflexes." By example he shows how closely the neurodynamics of schizophrenia approach the neurodynamics of the nervous system of an infant during the period when its nervous system is anatomically immature, i.e., before cerebral neuromic development is complete.

Socialization failure and a loss of ability for conceptual ideation are the two universal manifestations of the schizophrenic reaction and are obviously inter-related, the one the overt representation of a physiologic disturbance in the highest cerebral centers.

The other manifestations of schizophrenia vary both in degree of severity and in type. The intellectual deficit may progress to the point of almost total amentia, and the patient presents a picture commensurate with that seen in severe organic disease of the nervous system. Marked disturbances of the autonomic nervous system occur as in catatonia, symptoms suggestive of hypothalamic involvement. Emotional disturbances may become marked with either emotional blunting, emotional inconsistency or euphoria dominating the picture. In some cases deterioration is progressive and in others the picture remains almost stationary for years. Delusions may be well-fixed and systematized or may be bizarre, variable and poorly systematized. Hallucinations may or may not be present, or if present may disappear or change in their form or in the sensory field in which they are experienced. Some patients may recover from an initial attack and never experience recurrence, others may have several attacks with remissions, and others may never recover from an initial attack.

The manifestations are so variable and unpredictable, indicating everything from the most mild to the most severe involvement of the nervous system, that one is led to believe that the term schizophrenia does not characterize a disease entity but a group of disturbances of the nervous system in which there is some similarity between basic symptoms, but which are physiologically related only as the diseases of the heart which produce cardiac decompensation are related. The analogy may be reversed. Just as any disease process capable of interfering with the normal metabolism of the heart muscle will produce cardiac decompensation, any factor which is capable of interfering with the metabolism of the cells of the higher levels of the nervous system is capable of producing the manifestations of schizophrenia, and the degree of severity of the process will determine the physiologic level to which the nervous system regresses. When we find some morphologic change in the cells of the nervous system as in senile psychoses, luetic infections, cerebral trauma, hereditary neuromic deficiencies of the

cortex, or tumors we do not call the illness schizophrenia even though the manifestations may be indistinguishable from those seen in schizophrenia.

Let us consider for a moment primary mental deficiency in which there is an actual deficiency of neurons in the premotor cortex. The behavior and test patterns of these cases show greater predictability, consistency, and leveling in test strata than any secondary types of mental deficiency, and we know that we are dealing with a reaction pattern in which those centers concerned with the higher levels of concept formation are inadequate. In the high moron or borderline cases we note the following differentials between the behavior of these patients and the "normal" person.

- 1 An inability to form concepts, i.e., an inability to synthesize past experience and new perceptual phenomena into new association systems which adequately meet the demands of society, an inability for conceptual ideation of a high order

- 2 A deficiency in judgment, primarily a manifestation of the above inadequacy

- 3 A lack of idealistic supervision of the sexual urge

- 4 A definite predominance of individualistic drives over communal drives

- 5 A deficient sense of moral (sociologic) responsibility

- 6 A juvenile type of cerebration

- 7 Emotional inadequacy

- 8 Socialization failure dependent upon an inability to adequately meet the intellectual demands of communal existence

We find here the *basic* manifestations of the schizophrenic process, the difference being that in one case the manifestations are obvious from early infancy and in the other they develop in an individual who once presented a picture of normal or relatively normal mental development and behavior.

The author recalls to mind cases of post traumatic psychosis in which the patients presented a typical schizophrenic reaction and in which autopsy revealed cellular destruction in the higher cortical centers. He has had cases of senile dementia which in a younger individual would have been diagnosed schizophrenia of the catatonic, hebephrenic, or paranoid type as well as a case of syphilitic meningo-encephalitis in a young male in whom the manifestations were so typically catatonic that permission for mectrazol therapy was obtained before the Wassermann and spinal fluid findings proved the true basic pathology. Every psychiatrist has seen cases of organic disease of the nervous system in which the diagnosis could well be schizophrenia if *there were not a definite etiologic factor to account for the change in personality and behavior*.

To what does this lead us? Only to the conclusion that the study of any mental disease must follow the scientific postulates of the study of any other disease and must be referred ultimately to the question of a dis-

turbance in the physiologic processes of the cells of the organ which is being attacked. The study of the schizophrenic reaction is not a matter of classifying symptoms and indulging in philosophical speculation as to their import, but in attempting to evaluate these symptoms in the light of the development, form, and function of the nervous system. Although the products of function of the nervous system, behavior and thought, are not measurable in milligrams per cent they are nevertheless a manifestation of the energy production and expenditure of the cells of the nervous system and must be so interpreted and evaluated.

SYNTHESIS

Assuming, as we do, that the schizophrenic reaction is the result of a disturbance of the normal function of the cells of the nervous system, we have certain tangible facts which, although they do not necessarily point to the specific etiologic factor, indicate the nature of the forces at work which result in this functional disturbance.

Much stress has been laid upon the "conflict situation" as an etiologic factor. We have attempted to show that the "conflict situation" is a normal situation to which every percipient being is subjected from the time he reaches physiologic maturity until such time as he is no longer called upon to adjust himself to his environment as a "free" being, and that these conflicts are the direct result of man's immature phylogenetic status. The eternal conflict between individualism and moral obligation in the determination of man's behavior in response to the biologic urges of hunger, self-protectiveness, and love is the universal heritage of man. If we are searching for the causes of mental illness we must go deeper.

We have further attempted to show that man's species-specific mechanism for adapting himself to his environment in such a manner as to best serve the biologic goals of life is a uniquely human cerebral cortex, the cells of which are not mature at birth and the development of which is progressive from birth to senility. The highest and most intricate and involved function of this cortex is the formulation, through neuronc associations, of concepts which compromise individualistic urges and the urges of moral obligation and result in behavior acceptable to the mores. In delineating the physiology of levels of nervous function, we have seen that the level of concept formation requires the greatest energy potential and energy supply of all levels of function, that old concepts, once established, function with less expenditure of energy, and that phylogenetically established circuits require less energy for function than higher cortical circuits.

In evaluating the symptomatology of the schizophrenic reaction we find that there is one universal manifestation, an inability to form those concepts of behavior which normally adjust the individual to his environment as a member of a communal type of existence. We find, also, that the schizophrenic's behavior reflects a juvenile type of mentation in its less

serious form and a distinctly atavistic and unhuman type of behavior in its severe form, and that the reaction pattern reflects a neurodynamic state found in childhood when the nervous system is anatomically and physiologically immature, i e when the cells of the highest centers of the cerebral cortex are not developed. The severity of the process determines the degree of return to lower functional levels, i e delusions follow in general the type of reaction found in the formative period when "precept" rather than "concept" mechanisms are in play (i e there is an incomplete synthesis of data) and incoherent thought processes mark a return to a juvenile level near or at that stage of nervous function when vocalization is possible but is incoherent. (The gradual return through fixity of thought to incoherent speech seen in progressive alcoholic saturation which gradually eliminates cortical function from the highest levels downward also exemplifies this "cutting out" of cortical dominance.)

We also found that the schizophrenic reaction is so variable in its superficial manifestations that one is led to believe that schizophrenia is not a disease entity but a grouping of illnesses with one common manifestation just as one groups various entities under the term mental deficiency. We find as well that organic destruction of the cells of the cerebral cortex, and those phylogenetically newest are most vulnerable to attack, results in a reaction often indistinguishable from the schizophrenic reaction.

From these observations we conclude that the schizophrenic reaction results from a basic metabolic disturbance of the cells of the cerebral cortex which excludes or depreciates the ability for concept formation from the total reaction pattern of the nervous system, and results in a more juvenile or atavistic reaction to the circumstances of the environment. We do not feel that the "withdrawal" from reality is a willful mechanism, but that it results from an inability to adequately adjust to reality because of a physiologic deficit in the highest levels of nervous function, and that the type of behavior noted, juvenile or atavistic, reflects the highest level of nervous activity of which the organism is metabolically capable.

What then produces this metabolic deficit?

In any system, mechanical or physiological, in which several units function in reciprocal arrangement, that unit which is weakest, most unstable, or subject to the greatest stress will be the first to break down under great stress, or will be the first to manifest malfunction if other units fail to carry on their specific functions by not contributing their full share of work to the total mechanism. In the hierarchy of organs and systems which constitute the human organism, the nervous system is the unifying factor in the total reaction, dominating and coordinating all organ activity and at the same time being supported by and depending for function upon the functional integrity of the units it controls. The "master" of the human nervous system lies in the highest centers of the cerebral cortex. From a biologic and functional standpoint the cells of the human cerebral cortex,

particularly those of the highest functional centers in the pre-motor areas, are the most vulnerable to attack, are the most unstable, and are subject to a greater stress than are the cells of any other part of the nervous system. Therefore, the malfunction of these cells may result from any one of three specific factors—a lack of functional potential (hereditary cellular weakness), direct attack by a destructive force, or a disturbance in the function of some other unit of the organism upon which these cells depend for their metabolic requirements. Further, the breakdown of function is most likely to occur at that period when these cells are called upon for their greatest effort, i.e. when the circumstances of reality result in serious conflicts which require the integration of many neuromic units into an adequate concept to solve the problem presented by the situation.

Those in close contact with schizophrenia are impressed by several distinct observations in case studies. It is seldom that in taking a history one is unable to unearth a conflict situation which may be considered a precipitating factor in the psychosis and to which members of the patient's family refer as the "cause" of the patient's "breakdown." Also, one is impressed by the unusual frequency of a history of an inadequate personality or constitution in the background of the patient previous to the actual development of the psychosis and the gradual evolution of the psychosis precipitated by a specific conflict situation. We may eliminate as an etiologic factor the conflict situation, for as we have seen such conflict situations are universal and do not always result in a psychosis when they occur. In the individual case, the conflict situation may be the precipitating factor, but is not the etiologic factor.

Cardiologists speak of cardiac compensation, work reserve and decompensation and refer directly to the functional potential of the muscle cells of the heart. They find that many hearts are functionally capable of carrying on under normal stress and demands, but have no reserve power to take care of excessive demands caused by physical strain. The heart then decompensates, i.e. the muscle cells fail to adequately carry on. We find the same mechanism in schizophrenics. Most frequently this psychosis develops in individuals who seem to be functioning at their "peak performance" level in meeting the ordinary situations in life, and when a serious conflict situation arises they lack the reserve to carry on under the added demands on the highest functional level of the nervous system. The "breakdown" is then manifested by a functional inadequacy of the cells of the highest functional centers of the cerebral cortex, those requiring the greatest energy supply and expenditure for adequate function, and the result is the schizophrenic reaction in which lower and less energy demanding levels of function dominate the reaction of the organism. On the basis of this interpretation we may say that of the forms of schizophrenia the paranoid reaction is the least severe and the catatonic the most severe form of functional breakdown, for

in the former the return to lower levels is least marked whereas in catatonia* the manifestations indicate a regression to the diencephalic level of control. It must be remarked that the diencephalon (hypothalamus), upon which so much emphasis has been recently placed, does not control the cerebral cortex, but is a "distributor for a more comprehensive hook-up" in which the cerebral centers are normally the point of impulse initiation. Obviously, if the cortical centers are not in full functional control, the hypothalamus will be released, partially or completely, from cortical control and manifestations of hypothalamic dominance will occur. In the least severe forms the return will be to a juvenile type of mentation, a less energy demanding level, and childhood † or juvenile engrams and mechanisms will be brought into greater dominance in the total reaction. Infantile impressions and training are not etiologic factors, but may serve to intensify the conflict in any given situation or may color the delusional pattern. Delusions in themselves indicate that the nervous system is functioning at a juvenile level. *The return to infantile or juvenile reactions is not purposeful but is a physiologic necessity.*

A second finding is less frequent than that of personality or constitutional inadequacy, namely, the history of some somatic illness occurring as a precipitating factor in the development of the schizophrenic reaction. Here the pathogenesis should be obvious—a debilitating illness which deranges metabolism and homeostasis, the point of functional inadequacy developing at the weakest point in the entire structure—the cerebral cortex.

Less frequently we find the schizophrenic reaction developing in an adequate personality in which there is apparent no somatic deficiency factor to explain the reaction. The "conflict situation" will be elicited almost without fail, and the "break" is usually acute. We can explain this only as a direct functional depletion of the potential of the cells of the cortex in response to the excessive demands of the situation.

In other organs, e.g. the pancreas, functional derangements in the cells often result in permanent and progressive destruction or may be temporary. If we apply this same physiological fact to the cells of the nervous system we have a rational explanation upon which to interpret the fact that the prognosis in schizophrenia is so variable. It explains the progressive deterioration, suggestive of organic damage in some cases, the temporary duration of the psychosis in others, and the repeated attacks with remissions in others.

CONCLUSIONS

A correlation of data presented leads us to the conclusion that the schizophrenic reaction results from a basic metabolic disturbance of the neurons.

*The return to catatonia in many catatonics does not controvert this argument but merely shows that the sensory mechanism may be intact but the association centers are unable to organize the impulses to affect motor response.

†Percepts are held in one because of the fixity of their circuits and the fewer neurons involved require less energy expenditure for function than concepts which require polarization of a greater number of neurons for inclusion in the circuit.

of the cerebral cortex, that the biologic factor in the pathogenesis of the reaction is man's immature phylogenetic status, that the hereditary factor is the determining factor in the development of the reaction, and that the developmental (environmental) factor determines in part the manifestations of the reaction. We further conclude that schizophrenia is not a specific disease entity but a reaction pattern which may result from any cause which directly affects the functional potential of the cells of the cerebral cortex and that in the main there are three specific mechanisms which will produce the reaction.

- 1 An inadequacy state with lowered functional potential of cortical neurons in which the organism must function at full functional potential to carry on in the face of the ordinary stress and strain of life and in which there is no reserve for serious emergencies
- 2 Debility of the cortical neurons brought about by some abnormal somatic process
- 3 Depletion of the functional potential of the cortical neurons

BIBLIOGRAPHY

- 1 TREDGOLD, A F Mental deficiency, 5th Ed, 1929, Wm Wood & Co, Baltimore, Md
- 2 RIBBLE, MARGARETHE A Clinical studies of instinctive reactions in new born babies, Am Jr Psychiat, 1938, xcv, 149-160
- 3 BOLTON, J A contribution to the localization of cerebral function, Brain, 1910, xxxiii, 26
- 4 KARLIN, I W, and KENNEDY, L Delay in the development of speech, Am Jr Dis Child, 1936, li, 1138-1149
- 5 LEVIN, MAX Misunderstanding of the pathogenesis of schizophrenia, arising from the concept of "splitting," Am Jr Psychiat, 1938, xciv, 877-889

PLASMA CREATININE DETERMINATION AS A TEST OF LOW GRADE KIDNEY DAMAGE *

By AARON ARKIN, PH D , M D , F A C P , HANS POPPER, M S , M D †
and FRED A GOLDBERG, M D , *Chicago, Illinois*

WHEREAS there are well established methods of determining definite kidney insufficiency, the detection of low grade kidney damage by simple methods is still a problem. The purpose of this study is to show the value of plasma creatinine determination by newer methods, in the solution of this question.

In kidney damage the glomerular function is usually the first to be impaired as indicated by reduction of glomerular filtration. The original method of Rehberg¹ who used the exogenous creatinine clearance as a measure of glomerular filtration has been discarded, since in man creatinine is secreted when the blood level is artificially raised². The inulin clearance is now considered the most reliable measure of glomerular filtration. The endogenous creatinine clearance⁴ gives similar results⁵. Despite criticism of the theoretical value of the endogenous creatinine clearance as a measure of glomerular filtration⁶ its determination may be of clinical importance because of the simplicity of the technic.

Since endogenous creatinine is filtered through the glomerular loops and is probably under normal conditions neither secreted nor absorbed in the tubular part, any disturbance of the glomerular filtration causes retention of creatinine in the blood. The glomerular filtration undergoes physiological variations, whereas the blood creatinine level remains relatively constant.⁷ For clinical purposes, therefore, the blood creatinine determination is as informative as, and in some respects superior to, the time-consuming determination of glomerular filtration. A mild reduction of the urea filtration is compensated by reduction of the physiological urea reabsorption in the tubules. A reduction of the creatinine filtration cannot be compensated.

Some changes in the chemical technic and the use of newer optical instruments (examination by monochromatic light) have rendered the colorimetric determination more sensitive, an accurate determination at the normal blood level is now possible.⁸ In low grade renal insufficiency the results obtained are for this reason not in agreement with those obtained by older methods.

There is a disagreement as to the nature of the substances in the blood giving the creatinine color reaction⁹. There is, however, some creatinine present under normal conditions. The amounts found with the new method are in agreement with those obtained by more specific reactions¹⁰. Some

* Received for publication April 25, 1944.

From the Cook County Hospital (Medical Service of Dr. Aaron Arkin) and the Cook County Graduate School of Medicine, Chicago, Illinois.

† Research Fellow, Cook County Graduate School of Medicine.

results obtained with this method have been published¹¹ The following study substantiates these results

METHOD⁸ AND MATERIAL

Reagents (1) Saturated picric acid solution The picric acid crystals are purified according to Benedict¹² (2) 10 per cent sodium hydroxide, chemically pure

Four c c of oxalated plasma are added drop by drop to 12 c c of picric acid The test tube is shaken and immersed in a boiling water bath for 15 seconds The mixture is filtered through a Whatman filter No 44 To 10 c c of the cooled filtrate 0.5 c c of sodium hydroxide is added The mixture is filtered again through another Whatman filter to clear additional turbidity The colored solution formed is read with monochromatic light with a filter of 530 millimicron 20 minutes after the addition of sodium hydroxide The determination is made with either (1) a colorimeter, with artificial light and with a gray solution (Leitz) as a standard (depth of column of the unknown is 50 mm), or (2) with a photometer (depth 60 mm, instead of plasma, water added to picric acid and sodium hydroxide is used for compensation), or (3) with a photoelectric colorimeter¹³

Using a known creatinine solution, a comparison curve is made in the range between 0.5 and 3.0 mg per 100 c c If the creatinine concentration exceeds this range the plasma is diluted with water The normal level lies between 0.60 and 0.95 mg per 100 c c It is constant in normal individuals on different days or different times of the day Food or fluid intake is without influence Any increase over 1.0 mg per 100 c c, even as slight as 1.05 mg per 100 c c, is a probable sign of disturbed glomerular filtration

The material consists of 278 patients, many of them examined several times (474 examinations) In the table the cases are recorded with the highest creatinine level obtained Patients without kidney disturbances or without diseases commonly associated with extrarenal azotemia are not included in this study The creatinine concentration in the plasma of normal individuals has been reported previously¹¹

FINDINGS

Acute Glomerulo-Nephritis The 26 patients with acute glomerulonephritis show different stages of the disease (table 1) In 74 per cent an increase of the creatinine level over the normal was observed and only in one case did the level exceed 1.40 mg per 100 c c In 7 cases the return to normal was followed, whereas in the other cases with increase only single examinations were available The fact that in many cases a normal creatinine level was obtained and in others a decrease of the creatinine was observed led to an average of 1.05 mg per 100 c c

TABLE I
Plasma-Creatinine Values in Pathological Cases

Diagnosis	Number of Cases	Number of Examinations	Maximum Creatinine, mg %	Minimum Creatinine, mg %	Average Creatinine, mg %	Percentage of Cases with Blood Creatinine		
						Below 1 mg %	1 to 1.4 mg %	Above 1.4 mg %
Acute nephritis	26	56	1.44	.45	1.05	26.9	69.2	3.9
Extraglomerular acute nephritis	1	2	37.10	37.10	37.10	0	0	100.0
Transitional stage between acute and chronic nephritis	3	3	2.60	1.33	2.16	0	33.3	67.7
Acute exacerbation of chronic nephritis	2	5	24.80	1.14	9.36	0	0	100.0
Chronic nephritis	33	67	26.08	1.01	6.06	0	18.2	81.8
Nephrosis	12	27	2.60	.62	1.32	16.7	66.7	16.6
Amyloidosis	1	1	1.76	1.76	1.76	0	0	100.0
Benign nephrosclerosis	73	115	4.20	.49	1.24	34.2	34.2	31.6
Malignant nephrosclerosis	24	43	17.10	1.15	4.18	0	8.3	91.7
Polycystic kidneys	1	3	1.99	1.89	1.94	0	0	100.0
Obstruction of urinary passages	19	40	15.85	.80	4.95	15.8	15.8	68.4
Pyelitis	9	12	1.07	.76	.89	77.8	33.2	0
Extra-renal azotemia heart failure	26	35	1.91	.70	1.05	38.2	46.3	15.5
Pneumonia	5	5	1.22	.45	.98	60.0	40.0	0
Liver disease	27	34	16.52	.56	2.15	33.3	29.6	37.1
Hypochloremia	9	15	7.60	.76	1.95	11.1	33.4	55.5
Diabetic acidosis	5	5	4.28	1.04	2.58	0	20.0	80.0
Miscellaneous	2	6	3.36	.93	1.50	0	50.0	50.0
Total	278	474						

The non-protein nitrogen in all these cases was normal or just above the upper limit of normal. All cases recovered clinically.

In one case of acute extraglomerular nephritis with rapid downhill course a very high creatinine level was observed. Here the postmortem examination revealed extensive proliferation of Bowman's capsule with compression of the glomerular loops. In three cases of acute nephritis in which the transition to the chronic stage was observed the creatinine was much higher than in the cases with complete recovery, the average being 2.43 mg per 100 cc.

In several cases the creatinemic elevation was concomitant with a normal blood pressure.

Chronic Nephritis. In all cases of chronic nephritis an elevation of the creatinine level was found, up to 26.08 mg per 100 cc. In 18 per cent of the cases a moderate creatinine elevation was present, with a very slight increase in the non-protein nitrogen, a normal blood pressure and only a few red cells in the urine. In two cases of acute exacerbation of a chronic nephritis the creatinine increase was marked.

Nephrosis. In 10 of 12 cases of nephrosis a moderate increase of the

creatinine level was seen (average 1.32 mg) whereas the non-protein nitrogen and the blood pressure were normal. Clinically, no difference between these and the two cases with normal creatinine was noted. One case of amyloidosis revealed a high creatinine level.

Nephrosclerosis One third of the cases of benign nephrosclerosis showed a normal creatinine, another third a moderate increase of the creatinine level. In the remainder the creatinine was above 1.4 mg. The first group revealed normal non-protein nitrogen, the second normal or borderline figures. In malignant nephrosclerosis the creatinine increase was much higher and present in all cases. The average was 4.18 mg per 100 c.c. in contrast to 1.24 in benign nephrosclerosis.

Urologic Conditions In one case of polycystic kidneys a moderate increase of the creatinine was encountered. In most of the cases of obstruction of the urinary passages such as nephrolithiasis, prostatitis, and pyelonephritis, a definite increase of the creatinine level was found. In pyelonephritic contracted kidney the creatinine increase was as marked as in the primary or the nephritic contracted kidney. In pyelitis a normal value or slight increase was found.

Extrarenal Azotemia In this group cases were gathered with signs of nitrogenous retention but without obvious kidney pathology. In decompensated heart failure or pneumonia a moderate creatinine increase was observed. There were other cases of acute hepatitis, cirrhosis, or of obstructive jaundice of long duration which usually showed a definite creatinine elevation. An associated kidney involvement, however, has to be considered in a number of cases.

Instances of hypochloremia were observed associated with pyloric and intestinal obstruction, gastroenteritis with diarrhea and vomiting, and carcinoma of the pancreas. The increase of the creatinine level was evident in these cases although it was not as striking as the non-protein nitrogen increase.

In diabetic acidosis a creatinine increase was seen. The chemical determination, however, was less reliable, since acetone and acetoacetic acid may increase the color reaction.⁵

Under the miscellaneous group a case of Hodgkin's disease and one of bleeding peptic ulcer were included, each showing a moderate creatinine and definite non-protein nitrogen increase.

Creatinine and Non-Protein Nitrogen of the Plasma In figure 1 creatinine and non-protein nitrogen are plotted against each other. For the normal cases we refer to a similar graph in our previous study.¹⁰ In the range over 1 mg of creatinine per 100 c.c. many cases were found with normal non-protein nitrogen, indicating the greater sensitivity of the creatinine test. In the cases with more marked creatinine increase there is a difference between renal and extrarenal azotemias. In renal azotemia the creatinine increase is much higher in comparison with the non-protein nitrogen increase,

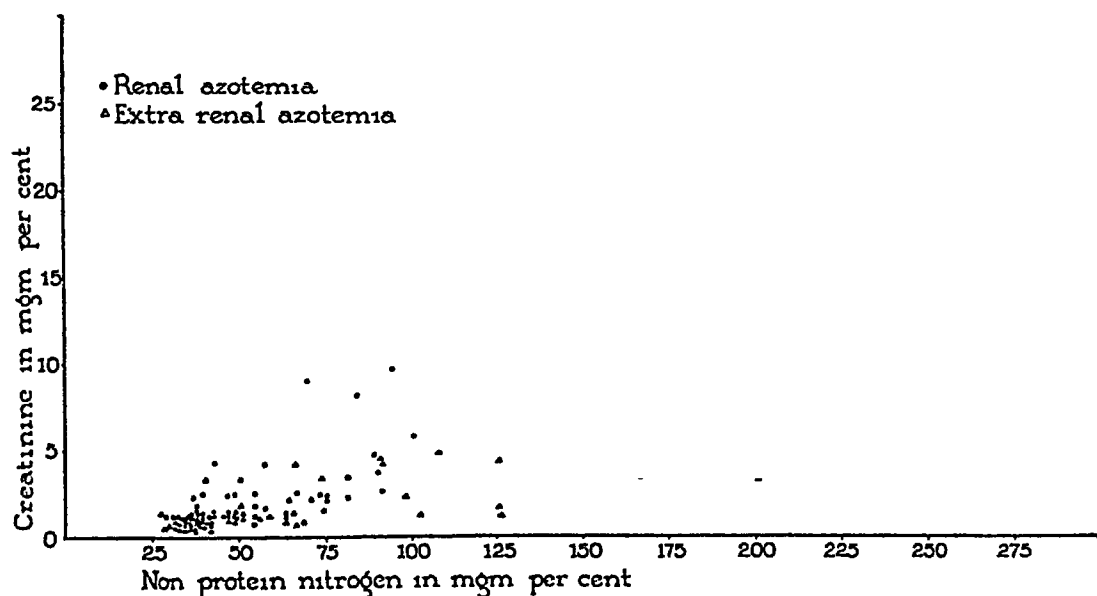


FIG 1

than in cases of extrarenal azotemia. The few cases of extrarenal azotemia with relatively high creatinine increase were patients with jaundice in which a nephritic component was either suggested clinically or proved at autopsy.

Relation of Plasma Creatinine to Hypertension and Albuminuria. The plasma creatinine usually runs parallel with the blood pressure and the degree of albuminuria (table 2) in the cases of hypertensive kidney diseases (essential hypertension, benign and malignant nephrosclerosis). In the other pathological cases (nephritides, urologic conditions, extra-renal azotemia)

TABLE II

Correlation between Plasma Creatinine and Blood Pressure or Albuminuria in Pathological Cases. The Hypertensive Kidney Diseases are Separated from the Other Cases

Hypertensive	Number of Cases	Maximum Creatinine	Minimum Creatinine	Average Creatinine
B.P. below 150	1	1.02	1.02	1.02
B.P. between 150-180	7	2.32	1.12	1.40
B.P. between 180-220	28	17.1	.59	3.27
B.P. above 220	11	15.0	1.08	4.00
Urine—0	9	2.50	.59	1.82
Urine—One Plus	15	8.35	.60	2.34
Urine—Two Plus	9	11.30	1.15	2.56
Urine—Three Plus	11	17.10	1.02	4.66
Non Hypertensive				
B.P. below 150	40	16.52	.15	2.93
B.P. between 150-180	12	10.85	.69	2.52
B.P. between 180-220	14	21.80	.78	4.76
B.P. above 220	1	26.08	2.03	10.07
Urine—0	11	1.22	1.01	1.17
Urine—One Plus	18	16.52	.45	3.70
Urine—Two Plus	15	8.45	.62	2.43
Urine—Three Plus	21	26.05	.56	5.19

with and without hypertension, this parallelism is not so obvious except that high grade hypertension is usually combined with very high creatinine levels

DISCUSSION

The clinical value of the plasma creatinine determination lies in the low ranges, the increase probably indicates a slightly disturbed glomerular filtration. The test in these ranges is superior to the determination of the non-protein nitrogen and urea not only for theoretical reasons (lack of reabsorption in the tubules) but also because of the sharper limits between normal and pathological range, and because of the lesser influence of extrarenal factors such as alimentary intake or protein breakdown.

In the following instances the demonstration of mild glomerular filtration damage is of diagnostic importance

(1) In acute glomerulonephritis the slight creatinine increase may be helpful in the diagnosis, although a normal creatinine level does not exclude the diagnosis. The creatinine increase is especially significant in oligosymptomatic forms. It may be an early sign of acute nephritis and has the same diagnostic significance as hematuria, edema, or hypertension. It should be sought in the convalescent stage after tonsillitis or other acute infectious diseases. The degree of the increase is significant. If the level lies above 1.4 mg per 100 cc the probability of a transition into a chronic nephritis is present. An extreme increase speaks for extraglomerular nephritis with poor prognosis as to life.

(2) In some mild forms of chronic nephritis with otherwise unexplained albuminuria, headaches or slight anemia, but without hypertension, concentration impairment, or definite non-protein nitrogen increase, the slight creatinine elevation may be helpful in classifying the case. The diagnosis of chronic nephritis may instigate a search for a suppurative focus.

(3) According to the newer theories of nephrosis¹⁴ a changed glomerular permeability is the underlying pathological process (membranous nephritis). The morphological changes in the tubules are secondary, due to reabsorption of proteins and fats which have escaped through the damaged glomeruli. In most cases the nephrosis is a consequence of a nephritic process with at least transitory impairment of the glomerular filtration (proliferative nephritis). The filtration damage is usually not extensive enough to cause non-protein nitrogen or urea increase, but is indicated by slightly elevated creatinine. Only a few cases of nephrosis are absolutely free of any nephritic symptoms, as shown by normal creatinine levels. The creatinine determination is more sensitive than that of urea or of non-protein nitrogen in the detection of a nephritic component in nephrosis.

(4) In the hypertensive kidney diseases the creatinine determination permits a differentiation between the essential hypertension without kidney involvement and the benign nephrosclerosis with slight kidney involvement. In the latter type the glomerular function damage and the impaired blood

flow may be due to primary vascular changes in the kidney or to cardiac decompensation. In decompensated cases successful cardiac management decreases the creatinine level

(5) In urologic conditions the creatinine increase is an early sign of parenchymatous kidney damage

(6) In extrarenal azotemias two possibilities are present. First, a moderate creatinine increase with normal or nearly normal non-protein nitrogen as seen especially in decompensated heart failure, with consequent improvement after successful cardiac management. The slight glomerular filtration damage is due to reduced blood flow. A reduction of the urea filtration is compensated in contrast to that of creatinine. The creatinine elevation indicates the degree of congestion in the kidney. A differentiation from similar creatinine increases in acute nephritis, nephrosis, or benign nephrosclerosis is nearly always possible with the help of other findings

In a second group of diseases usually associated with extrarenal azotemia, such as hypochloremia, liver diseases, or diabetic acidosis, the increased non-protein nitrogen is out of proportion to the normal or slightly increased creatinine. The hypothesis may be offered that the filtration damage is less significant than a pathologically increased reabsorption of nitrogenous substances through the damaged tubules. The backflow of urea is more extensive than that of creatinine.¹⁵ In nephritis the functioning nephrons reveal intact tubular epithelium, consequently the reduced glomerular filtration is compensated by reduced tubular reabsorption.¹⁰ In extrarenal azotemia, fairly normal glomeruli are connected with damaged tubules (e.g. icteric nephrosis) and a reabsorption uremia is possible (disorganization of kidney function in diabetes¹⁷)

Except for these already known differences¹⁸ between renal and extrarenal azotemia, the creatinine determination offers no advantages over the determination of other nitrogenous substances, in the higher creatinine ranges. The theoretical objections against the endogenous creatinine clearance as a measure of glomerular filtration are especially valid for the high creatinine ranges in which reabsorption or secretion of creatinine in the tubules may be considered

SUMMARY AND CONCLUSIONS

The application of a new simple determination for plasma creatinine provides a helpful diagnostic procedure for the detection of mild disturbances of glomerular filtration and, consequently, of low grade kidney damage. The demonstration of these disturbances is of diagnostic and prognostic importance in acute nephritis, chronic nephritis, nephrosis, nephrosclerosis, urologic conditions and heart failure. In extrarenal azotemia (hypochloremia and liver disease) the increase of the creatinine level is relatively less marked than that of urea and non-protein nitrogen apparently due to increased reabsorption of urea

REFERENCES

- 1 REHBERG, P B Studies on kidney function, *Biochem Jr*, 1926, xv, 445-460
- 2 (a) SMITH, H W The physiology of the kidney, 1937, Oxford Press, New York
 (b) SHANNON, J A The renal excretion of creatinine in man, *Jr Clin Invest*, 1935, xiv, 403-410
 (c) MILLER, B F, and WINKLER, A W The renal excretion of endogenous creatinine in man, comparison with exogenous creatinine and inulin, *Jr Clin Invest*, 1938, xvii, 31-40
- 3 (a) RICHARDS, A N, WESTFALL, B B, and BOTT, P A Renal excretion of inulin, creatinine, xylose in normal dog, *Proc. Soc. Exper Biol and Med*, 1934, xxxii, 73-75
 (b) MILLER, B F, ALVING, A S, and RUBIN, J The renal excretion of inulin at low plasma concentration of this compound and its relationship to the glomerular filtration rate in normal, nephritic and hypertensive individuals, *Jr Clin Invest*, 1940, xix, 89-94
- 4 POPPER, H, and MANDEL, E Filtrations- und Resorptionsleistung in der Nierenpathologie, *Ergebn d inn Med u Kinderh*, 1937, liii, 685-794
- 5 STEINITZ, K., and TURKAND, H The determination of the glomerular filtration by the endogenous creatinine clearance, *Jr Clin Invest*, 1940, xix, 285-298
- 6 (a) ALVING, A S, and MILLER, B F A practical method for the measurement of glomerular filtration rate (inulin clearance), *Arch Int Med*, 1940, lxxvi, 306-318
 (b) SMITH, H W Kidney, *Ann Rev Physiol*, 1939, i, 503-528
- 7 POPPER, H, and BROD, J Die physiologischen Schwankungen der Nierenarbeit, *Ztschr f klin Med*, 1938, cxxxiv, 196-223
- 8 POPPER, H, MANDEL, E, and MAYER, H Zur Kreatininbestimmung im Blut, *Biochem Ztschr*, 1937, ccxci, 354-367
- 9 SMITH, W W, FINKELSTEIN, N, and SMITH, H W Renal excretion of hexitols (sorbitol, mannitol, and dulcitol) and their derivatives (sorbitan, isomannide and sorbide) and of endogenous creatinine-like chromogen in dog and man, *Jr Biol Chem*, 1940, cxxxv, 231-250
- 10 MILLER, B F, and DUBOS, R Determination by a specific, enzymatic method of the creatinine content of the blood and urine from normal and nephritic individuals, *Jr Biol Chem*, 1937, cxxi, 457-464
- 11 POPPER, J, MANDEL, E, and MAYER, H Die diagnostische Bedeutung der Plasma-kreatininbestimmung, *Ztschr f klin Med*, 1937, cxxxiii, 56-77
- 12 BENEDICT, S R A note on the purification of picric acid for creatinine determination, *Jr Biol Chem*, 1929, lxxxii, 1-3
- 13 HOFFMAN, W S Photometric clinical chemistry, 1941, W Morrow and Co, New York.
- 14 BELL, E T Clinical and pathological study of subacute and chronic glomerulo-nephritis including lipid nephrosis, *Am Jr Path*, 1938, xiv, 691-736
- 15 MEYER, K A, POPPER, H, and STEIGMANN, F Significance of rise of nonprotein nitrogen in surgical and medical jaundice, *Jr Am Med Assoc*, 1941, cxviii, 847-850
- 16 ARKIN, A, and POPPER, H Urea reabsorption and relation between creatinine and urea clearance in renal disease, *Arch Int Med*, 1940, lxxv, 627-637
- 17 McCANCE, R. A., and WIDDOWSON, E M Functional disorganization of the kidney in disease, *Jr Physiol*, 1939, xcv, 36-44
- 18 FISHBERG, A M Hypertension and nephritis, 4th ed, 1939, Lea and Febiger, Philadelphia

HUNNER ULCER OF THE BLADDER (REVIEW OF 100 CASES) *

By CHARLES C HIGGINS, M D , *Cleveland, Ohio*

IN 1836, Mercier ¹ first mentioned ulcerations of the floor of the bladder causing perforation. Lawson Tait ² in 1870 discussed a similar lesion and cited an additional case. Fenwick ³ in 1896 described in detail, "simple ulcer of the bladder," and mentioned the sudden onset of the disease characterized clinically by increased frequency of urination, dysuria, and intermittent hematuria.

As some confusion still exists as to the lesion which should be classified as a Hunner ulcer, it is of interest to refer to Hunner's original description in 1914 ⁴. He stated that the ulcer is found on the vertex, summit, or free portion of the bladder, in contrast to Fenwick's solitary ulcer which is observed on the base or fixed portion of the bladder. He further stated, "There is nothing absolutely characteristic in the cystoscopic picture. One's attention may be first arrested by slight, smooth, white scars of former ulceration rather than by the slight hyperemia or inflammatory spots near these scars." In other cases there is a small area of granulation which bleeds upon distention of the bladder or bleeds easily upon being touched. In certain instances, the same inflammatory spot is occupied and surrounded by an area of edema. Keene ⁵ in 1920 referred to this condition as circumscribed, panmural, ulcerative cystitis. Other authors have called it interstitial cystitis, elusive ulcer, panmural cystitis, submucous fibrosis, and submucous ulcer. In 1930, Bumpus ⁶ used the term, "interstitial cystitis," and stated, "As knowledge of the disease has grown, it has become apparent that the areas are frequently very extensive and not localized to any one portion of the wall of the bladder."

There is but little doubt that earlier urologists probably overlooked the so-called "Hunner ulcer" because they failed to overdistend the bladder. The condition, therefore, frequently was designated as "cystic neuralgia or neurotic bladder," and since it was overlooked so frequently the term "elusive ulcer" was ascribed to it. Hinman, ⁷ in 1939 favored calling this ulcer of the bladder a Hunner ulcer. In recent years, Kretschmer, ⁸ Folsom, ⁹ Peterson and Hager, ¹⁰ Young, ¹¹ Quinby, ¹² and others have published reports describing this lesion with its clinical manifestations.

ETIOLOGY

Hunner ⁴ observed the probable relationship between focal infection and Hunner ulcer of the bladder, the sites from which the infection was dis-

* J. Urol. 61: 705, 1948.

seminated being the teeth, tonsils and sinuses, the infection being carried to the bladder by the blood stream

Meisser and Bumpus,¹⁴ in 1921, stated, "if it is assumed that such cases of cystitis are of focal origin, instead of being invariably the result of an adjacent infection, many aspects of the disease can be explained. Under certain conditions the infecting organism may cause generalized cystitis or, if the inflammation becomes localized in one area of the bladder, necrosis of the mucosa will result in a simple ulcer of the bladder. The organisms may lodge deeper in the wall of the bladder. In such an event the pathologic process will occur entirely below the mucosa and that rare type of ulcer first described by Hunner results."

Kretschmer⁹ does not agree that Hunner ulcer occurs more frequently in women because of infection in the cervix and adnexa. In the 14 cases reported by Kretschmer, careful pelvic examinations were made but no pelvic pathology was found.

In a review of 110 cases, Hinman⁸ made a careful search for foci of infection. Of six men with Hunner ulcer, three had a positive history of gonorrhea and one had syphilis with a primary genital chancre. The most significant fact in this review, however, was that of the women from whom a detailed past history was elicited, 80 per cent had had pelvic inflammatory disease, induced abortions, ectopic pregnancies or marked menstrual disorders. Keene,¹⁵ in a report of the treatment of 25 cases, carefully eradicated all foci of infection, without procuring symptomatic relief in a single instance. In 1925, Peterson and Hager¹¹ questioned why organisms in foci common to both sexes should show a selective affinity for the bladder in women.

In our series, 58 per cent had demonstrable foci of infection in the teeth, tonsils, or cervix. Diseases of the upper urinary tract, such as pyelonephritis, hydronephrosis, or infected hydronephrosis, were present in 19 per cent. Three of the men had coexisting chronic prostatitis, and one had syphilis. Allergy was present in 19 per cent of the patients.

INCIDENCE

Hunner ulcer of the bladder is preponderantly a disease of women. Hunner especially emphasized the prevalence of the disease in the female sex. All of his series of 25 cases were in women. In Hinman's series of 110 cases, only six were observed in men. In 1931 Folsom⁷ cited a series of 20 cases of Hunner ulcer, of which 17 occurred in women and three in men. Kretschmer,⁹ in 1922, in his series of 14 cases, noted that the ulcer occurred in 13 instances in women. Of 15 cases of Hunner ulcer reviewed by Bumpus,⁶ 13 were in women. Peterson and Hager,¹¹ in 1707 urologic patients consisting of 1292 men and 415 women, reported the occurrence of Hunner ulcer in eight women.

In our group of 100 cases of Hunner ulcer, 94 occurred in women and six in men. The youngest patient was 18 years of age, and the oldest 77 years. The average age was 48 and a half years. All were in the sixth decade of life but two, who were 21 and 28 years of age respectively.

PATHOLOGY

The pathology in Hunner ulcer consists essentially of submucous inflammation of the bladder wall. Cellular infiltration occurs and, according to Peterson and Hager, nothing in the microscopic picture of the lesion is pathognomonic of the disease.

Young¹² states that the predominant pathological process is found in the deeper layers of the bladder wall. A portion of the loose areolar tissue of the submucosa has been replaced by fibrosis and the lesion may be very small. In instances where the lesion is circumscribed and confined to a small area of the bladder, the bladder wall itself shows little or no increase in thickness at the point of involvement. However, in other cases in which the inflammatory process has extended through all layers of the bladder wall and has involved the muscularis layer, considerable thickening of the bladder wall in the involved area may be observed. The mucous membrane overlying these lesions may be intact and may reveal edema or congestion. In other instances, linear ulcerations or small areas of scarring may be observed. From such a pathological process the mucous membrane becomes attached to the inelastic and dense underlying fibrotic area and causes tearing and bleeding of the mucous membrane when the bladder is overdistended.

The microscopic pathology is very similar to that of chronic cystitis except for the fibrosis in the submucosa. Varying degrees of round-cell infiltration are present beneath the fibrous lamella, and often between the muscle bundles as far as the serous layer. There may be increased vascularity with numerous newly formed capillaries in the submucosal layer. The characteristic pathologic lesion of the disease stated by Young, however, is a dense fibrosis which may involve the submucosa to varying degrees or, when more pronounced, may involve the muscularis layer.

This entity probably is overlooked frequently because widespread destructive processes can occur in the bladder without giving rise to proportional objective urinary findings. Hematuria is not an unusual finding, and was noted prior to treatment in 18 per cent of this series. Hinman reports similar observations in 110 cases. He states that the initial examination of the urine was negative for pus, blood or organisms in 22 instances and positive for one or more in 70.

In this series, red blood cells were observed in the urine in 58.1 per cent of the cases and pus cells in 61 per cent. Undoubtedly, the frequent and prolonged local treatment to the bladder before these patients entered the clinic for cystoscopic study accounts for such a high percentage of patients with pus in the urine. In 11 patients in this series there was premenstrual aggravation of the bladder symptoms. Other urinary symptoms such as urgency, tenesmus, burning, tenderness, and backache were not as frequent as the symptoms previously mentioned.

DIAGNOSIS

The diagnosis of Hunner ulcer is established by presumptive evidence in the history and cystoscopic visualization of the lesion.

Occasionally, because of the pronounced reduction in the bladder capacity which may not exceed 60 to 90 c c. of solution, the ulcer cannot be recognized. However, if spinal anesthesia is administered, the ulcer usually can be seen. The cystoscopic picture is variable and, to a large extent, depends upon the degree of healing present. In some instances, the lesion on the bladder wall looks like a crushed strawberry. In cases in which the ulcer is healed, a small white area which cracks and bleeds when the bladder is overdistended exposes the site of the lesion.

Usually the ulcer is located upon the apex or dome or the free portions of the bladder, and may be single or multiple. In our series, a single lesion was present in 71 instances, and multiple ulcers were observed in 29.

In patients with Hunner ulcer who complain of supra-pubic pain, the pain may be reproduced during cystoscopy by touching the ulcer with the tip of the ureteral catheter.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis usually is not difficult to make if characteristics of the lesion are kept in mind. Hunner ulcer may be confused with simple ulceration or an ulceration of tuberculous origin. Several characteristics, however, make possible an accurate diagnosis, namely, (1) the location of the ulcer on the apex, dome, or free portion of the bladder, (2) the absence of the excavation of a true ulcer, unless the lesion has been previously fulgurated, (3) the presence in tuberculous ulcer of renal tuberculosis or the finding of the tubercle bacilli in the urine by culture or by guinea pig inoculation.

As a rule, the surface of a Hunner ulcer is not covered with a deposit of salts as may be observed in incruusted cystitis, malignancy, and simple ulcer. Syphilis, although rare in any case as a cause of bladder ulcer, may be ruled out by complement fixation tests.

Acute cystitis is differentiated by the history, pyuria, and cystoscopic study. In extravescical lesions such as salpingitis, diverticulitis of the colon, or malignant growths, which adhere to the bladder wall and produce marked urinary symptoms, cystoscopic study reveals an area of inflammation on the bladder wall surrounded by bulbous edema. However, such a lesion does not closely simulate a Hunner ulcer and complete examination reveals the causative factor. Ulceration of the bladder following the application of radium to the cervix or vagina may produce symptoms resembling those of Hunner ulcer of the bladder. The patient may seek consultation years after the radium has been applied and cystoscopic study reveals ulcerations upon the base or the trigone of the bladder. In this group, the location of the ulcer and a history of previous radium therapy establishes the diagnosis. Careful inspection of the bladder and mild overdistention aid in establishing an accurate diagnosis of Hunner ulcer. As has been aptly stated, the lesion may be masked by prolonged medical treatment, or overlooked because of a coexisting cystitis.

TREATMENT

The treatment of Hunner ulcer of the bladder constitutes one of the most difficult procedures in urology. The ineffectiveness of any one type of treatment is attested by the numerous procedures being employed at the present time.

In his original communication, Hunner advocated the radical excision of the ulcer-bearing area of the bladder. Later, however, he advocated more conservative procedures and recommended electrocoagulation which produced startling results if only one area was involved in the bladder. As a rule, however, the relief of symptoms lasted only from six months to one year, and a second treatment was required.

Considerable care must be exercised in overdistending the bladder as rupture at the site of the ulcer may occur. Similarly, by repeated electrocoagulation of the lesion, the blood supply to the area may be impaired and subsequent treatment may cause slough and gangrene of the bladder wall. Both complications have been reported in the literature.

Pumpus⁸ reported a series of more than 100 cases treated only by distention of the bladder with fair results in every case but one. Peterson and Hager⁹ consider conservative treatment to be the method of choice; namely, transurethral electrocoagulation, overdistention of the bladder or a combination of the two procedures. It has been stated that the results from overdistention of the bladder have been as satisfactory as those secured by electrocoagulation of the ulcer. The question is raised as to whether or not the

increased scar formation following fulguration would be of any final benefit

In one case Quinby¹⁸ resected the presacral nerve and obtained definite relief of pain without affecting the ability of the bladder to hold urine

Howard¹⁷ has suggested the use of emetine hydrochloride - Hinman⁸ used this drug in three cases and stated that one patient was benefited In six of our cases in which the drug was prescribed marked alleviation of symptoms occurred in two instances

At the present time, the consensus of opinion is that many patients will be relieved by fulguration and by hydrostatic pressure A few will be cured completely, but the treatment may have to be continued at varying intervals of time for years

For complete relief in a small group of well selected cases in which the bladder capacity is reduced to practically nil, transplantation of the ureters into the bowel may be advocated

Folsom¹⁰ recommends subtotal resection of the bladder in patients with advanced Hunner ulcer and reports a series of experimental observations of regeneration of the bladder in dogs This operation has been performed in eight patients All have been relieved of their bladder distress, one case for 17 years, one for three years, and the remainder for from a few months to two years

He concludes, "We feel that subtotal cystectomy is a safe surgical procedure, that any very serious infection of the upper urinary tract is a definite contraindication, that it will completely relieve the patient of the intolerable bladder irritation and pain, that success will depend on a complete removal of all the mobile parts of the bladder, that a new functionally satisfactory bladder will be regenerated; that a certain number of patients so operated will have some degree of regurgitation to the upper urinary tract, that the fact of good functional and anatomical regeneration after subtotal cystectomy will encourage us to a wider use of this procedure in other serious lesions of the bladder, as in carcinoma"

TREATMENT AND RESULTS

In our series of cases many different types of treatment were employed In all cases a diligent search for foci of infection was instituted and such foci eradicated if present

In 69 patients fulguration combined with overdistention and irrigations of the bladder was employed In 49 cases the sharp pointed electrode was used, in 16 the ball electrode, and in four the type of electrode was not stated This treatment was preceded by one or more irrigations of the bladder to ascertain whether or not they would be of value in the individual case In the majority of instances fulguration of the ulcer and overdistention of the bladder were performed under either nitrous oxide or spinal anesthesia

Of this group, 17 were definitely cured; 10 were lost trace of in the follow-up period, and 14 were not improved. Three partial resections of the ulcer-bearing area of the bladder were performed later. One patient in whom this was done was greatly improved. The last patient had a recurrence of symptoms and, as a last resort, the ureters were transplanted into the bowel with a resultant cure.

In one case in this group, resection of the presacral nerve was done without relief of symptoms. Twenty-eight patients were improved, many having periods of freedom from distress for months after fulguration and overdistention. With recurrence of symptoms, relief again was afforded by repeated fulguration and overdistention. Nine patients were treated by irrigations and overdistention; two were cured, there was no follow-up in five, one was improved, and one became worse.

Three patients were treated by irrigation and instillation of 4 per cent argyrol at the time of the initial examination, but they failed to return for further treatment. One patient was given irrigations and instillations of 16 per cent gomenol with marked alleviation of symptoms.

Three patients had fulguration alone with moderate relief of symptoms. Two of the male patients were completely cured by eradication of the chronic prostatitis, one by prostatic massage and the other, having coexisting prostatic hypertrophy, by prostatectomy.

Ultraviolet irradiation was applied directly to the ulcer by means of a quartz tube conductor in two cases, with questionable improvement in symptoms.

Bilateral transplantation of the ureters was performed in four additional cases. One patient died of pneumonia 10 days after operation, and the remaining three patients were completely relieved of symptoms.

Five patients did not return for treatment after the diagnosis had been established and were referred to their family physician for treatment.

Two patients have received treatment too recently to be mentioned in the series.

CONCLUSIONS

Hunner ulcer is predominately a disease of women, although it may be observed in men.

In this series, it was a disease of middle life, the greater percentage of our cases occurring in the fifth decade.

Proof of infection should be eradicated in all cases.

The symptom complex of Hunner ulcer is diurnal and nocturnal frequency with associated dysuria and suprapubic pain. This group of symptoms was present in over 90 per cent of the patients in our series. The average bladder capacity in this series was 135 to 140 c.c., which indicates a markedly diminished capacity.

The treatment of choice in our series, as indicated by the results, is conservative treatment, followed by radical treatment only if this fails to afford relief

Fulguration of the ulcer with the electrode combined with overdistention of the bladder under anesthesia is the procedure of choice in our series

Transplantation of the ureters into the bowel should be employed only if all other conservative measures have failed to give relief

REFERENCES

- 1 MERCIER Ulceration et perforation spontanes de la vessie, *Gaz med de Paris*, 1836, 257-273
- 2 TAIT, LAWSON On the cure of the chronic perforating ulcer of the bladder by the formation of an artificial vesicovaginal fistula, *Lancet*, 1870, liv, 738
- 3 FENWICK, E H Ulceration of the bladder, 1900, J A Churchill, London, p 8
- 4 HUNNER, G L A rare type of bladder ulcer in women, report of 8 cases, *South Surg and Gynec.*, 1914, xxvii, 247-288
- 5 KEENE, F E Circumscribed pan-mural ulcerative cystitis, elusive ulcer (Hunner), *Ann Surg*, 1920, lxxi, 479-485
- 6 BUMPUS, H C, JR Interstitial cystitis, its treatment by overdistention of bladder, *Med Clin North Am*, 1930, xiii, 1495-1498
- 7 FOLSOM, A I Hunner's ulcer, *Texas State Jr Med*, 1932, xxvii, 718-721
- 8 HINMAN, FRANK Discussion, Interstitial cystitis, by PETERSON, A, and HAGER, B H *Calif and West Med*, 1929, xxxi, 267
- 9 KRETSCHMER, H L Elusive ulcer of the bladder, *Surg, Gynec and Obst*, 1922, xxxv, 759-765
- 10 FOLSOM, A I Personal communication
- 11 PETERSON, A, and HAGER, B H Interstitial cystitis, report of cases, *Calif and West Med*, 1929, xxxi, 262-267
- 12 YOUNG, H H Practice of urology, 1926, W B Saunders Co, Philadelphia, p 145
- 13 QUINBY, W C Resection of the presacral nerve in painful bladder of interstitial cystitis, *Trans Am Genito-Urin Surg*, 1931, xxiv, 355-361
- 14 MEISSER, J G, and BUMPUS, H C, JR Focal infections in relation to submucous ulcer of bladder and to cystitis, *Jr Urol*, 1921, vi, 285-298
- 15 KEENE, F E Elusive ulcer of bladder, *Am Jr Obst and Gynec*, 1925, x, 380-385
- 16 FURNISS, H D Fulguration of Hunner ulcers, *Am Jr Obst and Gynec*, 1924, vii, 288-291
- 17 HOWARD, T LEON Personal communication

A ROENTGEN STUDY OF CAVITIES IN PULMONARY TUBERCULOSIS; CAVITY CHANGES UNDER COLLAPSE AND NON-COLLAPSE MEASURES

By R C EDSON, M D , and A L STARKEY, M D ,
Hopemont, West Virginia

FREQUENTLY, the clinician's estimate of results over a period of years is at wide variance with actual results as tabulated by a definite statistical study of the same material. While mathematical calculations can never be applied specifically to any individual case in medicine, nevertheless, results of the past should be used as a rough guide in determining relative values for present decisions and prognostications. In an effort to aid in the evaluation of therapeutic results in cavernous tuberculosis, a study based on the interpretation of chest roentgenograms was initiated. The paper has been limited primarily to individual cavity changes and, therefore, cavity closure does not necessarily infer controlled tuberculosis.

Hospital records were examined of all patients admitted to Hopemont Sanitarium, Hopemont, West Virginia, from July 1925 to July 1938. No observations were extended beyond July 1939. A period of observation for at least one year after admission was thereby obtained.

Within limits, this is a study of selected cases and selected cavities. Only proved cases of tuberculosis with adequate roentgen studies and with at least six months of controlled therapy were used. All cases leaving the sanatorium or cases in which death occurred prior to the six month period were excluded. Only cavities with a complete roentgen outline were used. Although many early cavities, especially in the presence of exudative disease, did not show definite cavity walls most of these on later films became definite, showed complete cavity walls and were then included in the series.

The total number of usable cases was 750 and the total number of usable cavities in these cases was 1097.

Classification of cases with reference to sex and average age was made. There were 439 females and 311 males. The ratio of females to males was 59-41. The general admissions to Hopemont for the same year period show a ratio of 62-38. The average age for the females was 26, for the males 29, and the combined average age was 27. In both male and female the greater incidence of disease in the third and fourth decade is emphasized.

Classification of cases with respect to extent of disease has been made using the National Tuberculosis Association Classification as a standard. Differences in comparing results in tuberculosis therapy, not only in dif-

ferent institutions but also in the same institutions for different year periods, have been due largely to the wide variation of cases that may come under the classification of far advanced disease. Recognition of this fact has led the staff at Hopemont to adopt a modified classification¹. Under this grouping the National Tuberculosis Association Classification is applied separately to each side in addition to its usual application to the case as a whole. If there is sufficient disease on one side alone to make the case moderately advanced then that side is classified as moderate. Under the Standard Classification only 5 per cent of the cases in the study are moderately advanced whereas 95 per cent are far advanced. Under the Modified Classification it is further noted that 78 per cent of the cases fall into either the far and moderate or far and far advanced groups.

It is readily admitted that should an equal number of cases be studied composed of 95 per cent far advanced disease the results of similar therapy should not vary greatly. However, if in the one instance a high percentage of the far advanced cases is made up of moderate and moderate, far and clear, and far and minimal cases, and in the other instance a high percentage of the far advanced cases is made up of far and moderate, and far and far cases then the results would actually show wide variations.

Individual cavities have been measured in centimeters at the widest diameter on the 72 inch postero-anterior film and have been divided into the following five groups: 0-2 cm, 2-4 cm, 4-6 cm, 6-8 cm, 8 plus cm. In instances of multiple cavitation where it was impossible to follow individual cavities on consecutive films, the total diameter of the multiple cavitation was taken and considered as a single cavity. Cavities measuring exactly 2, 4, 6, or 8 cm were alternately placed in the higher and lower divisions.

THERAPEUTIC MEASURES

Roentgen changes in individual cavities were tabulated for patients on bed rest, mild activity, phrenic nerve surgery, pneumothorax, and thoracoplasty. By bed rest is meant absolute rest in bed for the entire 24 hours daily. Mild activity varies from one bathroom privilege daily to two hours exercise plus bathroom and dining room privileges. Phrenic nerve surgery includes permanent, temporary, and repeat procedures. By pneumothorax is meant intrapleural pneumothorax. Cavity changes were credited to pneumothorax even in the presence of pneumonolysis or combined phrenic surgery and pneumothorax procedures. Cavities were considered to be under pneumothorax until complete reexpansion of the lung was seen by roentgenogram. Thoracoplasty includes all cases in which ribs were removed for the purpose of obtaining collapse of the lung. Phrenic nerve surgery, pneumothorax and thoracoplasty actually consist of these procedures plus bed rest. Cavities were considered closed only when roentgen studies failed to reveal any evidence of open cavity. Blocked cavities occurred in 15 of the 750 cases, a 2 per cent case incidence. These cavities were considered

closed only when they were replaced by a dense homogeneous shadow which persisted throughout the remainder of the study. Only cavities that had a minimum of six months on any given therapy have been listed under that therapy. The same cavity if observed for six or more months under more than one procedure has been listed under each procedure. Thus, while the cavities present in this series total 1097, the therapeutic results for these cavities total 1333.

RESULTS OF THERAPEUTIC MEASURES

Results short of complete cavity closure are not satisfactory and yet it is of interest to determine changes in size under each procedure. A tabulation of all cavities showed 35 per cent of the cavities closing, 20 per cent becoming smaller, 17 per cent remaining the same and 28 per cent becoming larger. Cavities were closed or made smaller more frequently by collapse measures than by non-collapse measures (chart 2, graph 1).

In bilateral cavitation cases where collapse measures had successfully controlled one side, there were 29 open cavities on the opposite side. The following results were obtained on these 29 cavities under the various forms of therapy.

	Open	Closed
Bed rest	5	8
Mild activity	1	1
Phrenic surgery	1	1
Pneumothorax	0	12
Total	7	22

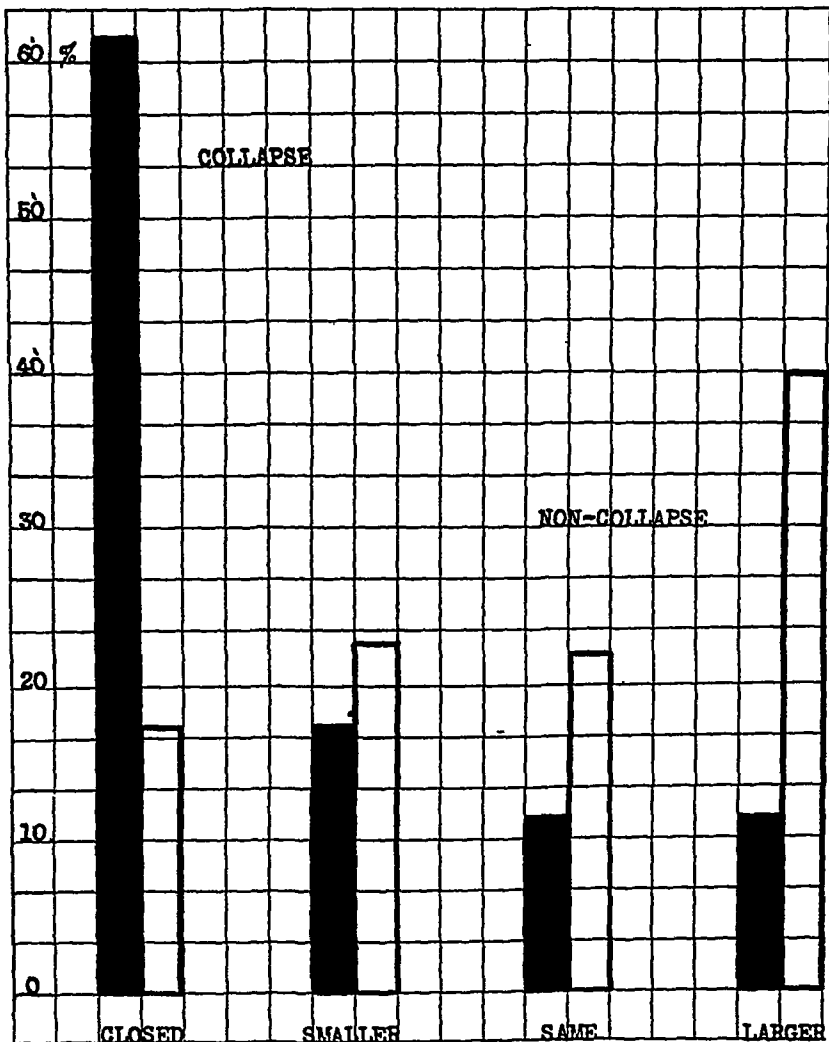
In the collapse therapy series combined collapse measures were used for 136 cavities and pneumonolysis was a factor in 32 cavities under pneumothorax. Phrenic nerve surgery, pneumothorax, and thoracoplasty were used for seven cavities, phrenic nerve surgery and thoracoplasty for eight cavities, and pneumothorax and thoracoplasty for one cavity. All of these 16 cavities were closed by thoracoplasty. There were 120 cavities treated by phrenic nerve surgery and pneumothorax. Of this number 24 remained open and 96 were closed. Under pneumothorax plus pneumonolysis three cavities remained open and 20 were closed.

CHART I
Distribution of Cavities

Therapy	0-2 cm	2-4 cm	4-6 cm	6-8 cm	8 plus cm	Total
Bed rest	28	126	130	78	165	529
Mild activity	13	78	71	49	53	264
Phrenic surgery	3	33	48	29	56	169
Pneumothorax	11	70	140	15	75	311
Thoracoplasty	0	1	10	5	14	30
Neurolysis	41	206	291	127	218	793
Collapse	14	104	106	79	115	540
Total	55	316	399	265	363	1333

CHART II
Therapy Results in Unclosed Cavities

Cavity Size	Smaller			Same			Larger		
	Non Coll	Coll	Total	Non Coll	Coll	Total	Non Coll	Coll	Total
0-2 cm	1	1	2	4	0	4	19	1	20
2-4 cm	41	12	53	30	10	40	73	7	80
4-6 cm	40	18	58	42	14	56	86	17	103
6-8 cm	33	20	53	23	10	33	53	12	65
8 plus cm	58	39	97	72	27	99	81	22	103
Total	173	90	263	171	61	232	312	59	371
Per cent	22	17	20	21	11	17	40	11	28



GRAPH 1 Cavity results—collapse versus non-collapse in 1333 cavities

CAVITY CLOSURE

A study of the cavities closed under therapy calls attention to a number of important considerations. There were 529 cavities on bed rest, 264 on mild activity, 169 on phrenic nerve surgery, 341 on pneumothorax, and 30 on thoracoplasty. Cavity closure occurred more frequently in the smaller cavities under every mode of therapy. The percentage of closed cavities under bed rest therapy is 13 and that obtained under mild activity is 25. The greater preponderance of exudative disease and the larger total cavitation present in the cases on bed rest are in great part responsible for this discrepancy. Phrenic nerve surgery resulted in 24 per cent cavity closure, pneumothorax 76 per cent, and thoracoplasty 93 per cent. The unusual results of thoracoplasty are due to conservative selection of cases for this procedure. Since, however, the total number of thoracoplasty cases included is but 30 in a series of 1333 therapeutic results their influence on percentage is slight.

CHART III

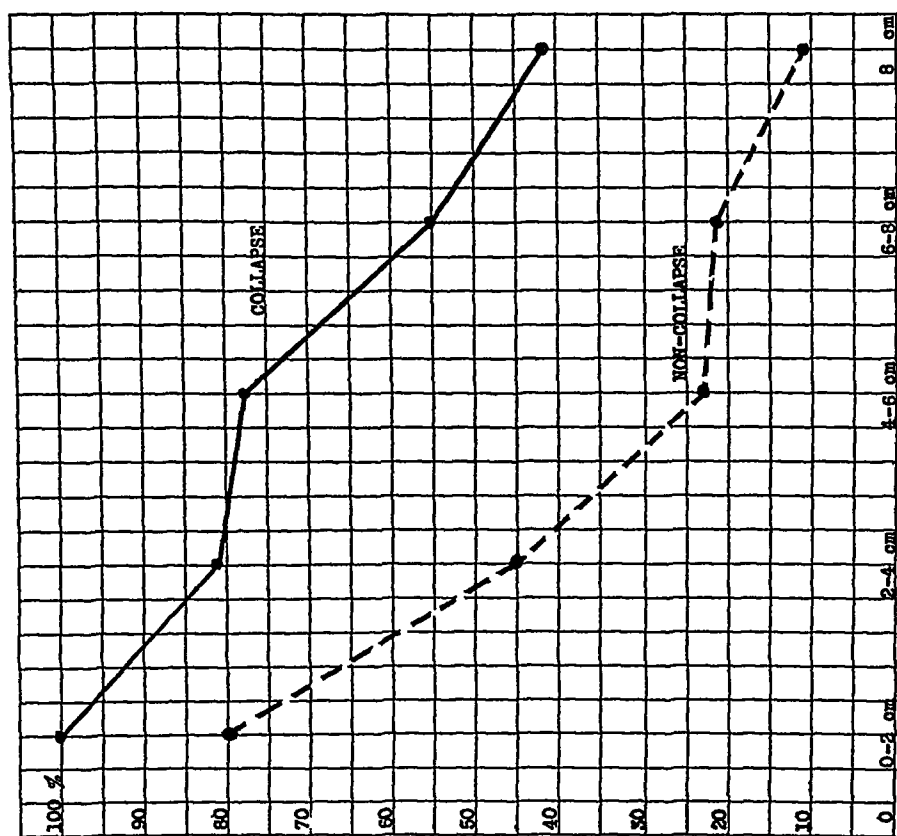
Cavity Closure

A Study of 1097 Cavities with 1333 Therapy Results

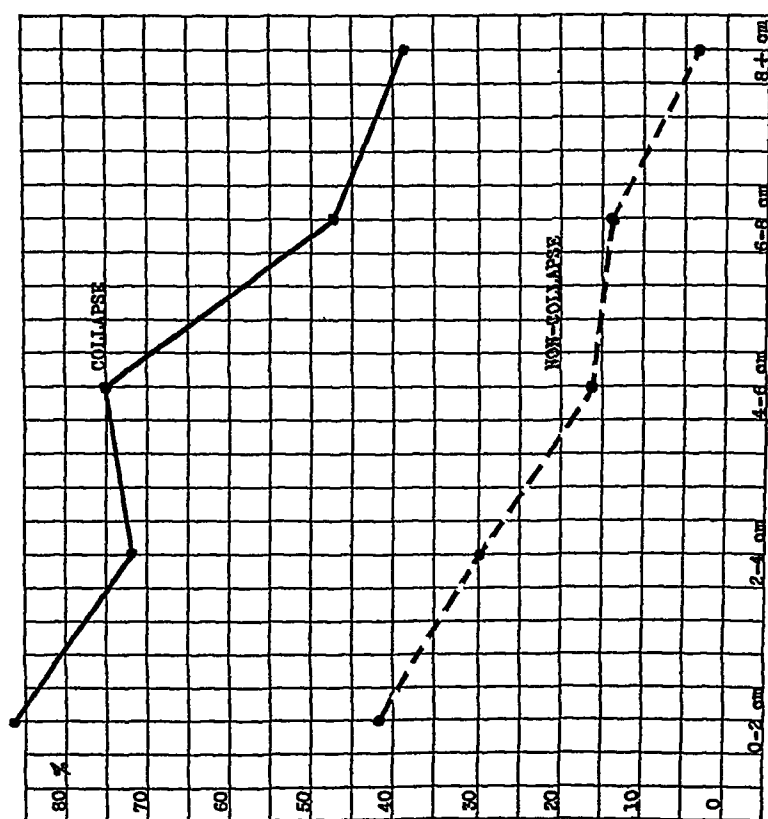
Therapy	0-2 cm		2-4 cm		4-6 cm		6-8 cm		8 plus cm		Total	
	No Closed	% Closed	No Closed	% Closed	No Closed	% Closed	No Closed	% Closed	No Closed	% Closed	No Closed	% Closed
Bed rest	8	28	33	26	17	13	10	13	3	2	71	13
Mild activity	9	69	29	37	16	22	8	16	4	8	66	25
Phrenic surgery	2	66	13	39	20	42	3	10	4	7	42	24
Pneumothorax	10	91	61	87	119	85	30	67	40	53	260	76
Thoracoplasty	0	0	1	100	10	100	4	80	13	93	28	93
Non-collapse	17	42	62	30	33	17	18	14	7	3	137	17
Collapse	12	86	75	72	149	75	37	47	57	39	330	61
Total	29	53	137	44	182	45	55	21	64	17	467	35

If the 793 cavities on bed rest and mild activity are compared with the 540 cavities on phrenic surgery, pneumothorax, and thoracoplasty, it will be noted that in the non-collapse series closure occurred in 137 cavities, a total of 17 per cent. In the collapse series closure occurred in 330 cavities, a total of 61 per cent. Furthermore, in the non-collapse group the percentage of closures ranges from 42 per cent in the 0-2 cm cavities to 3 per cent in the cavities over 8 cm. The collapse group ranges from 86 per cent to 39 per cent for similar diameters (chart 3, graph 2).

It seems logical to assume that a cavity which represents the total pulmonary cavitation will close more readily than a similar cavity which represents only a part of the total cavitation, therefore a separate study of the 457 cases with single cavitation was also made. There were 573 therapeutic



GRAPH 3 Cavity closure in 573 Single cavitation cases



GRAPH 2 Cavity closure—collapse versus non-collapse in 1333 cavities

results in this series Closure was accomplished in 65 of the 245 cavities under non-collapse measures, or 26 per cent, and in 216 of the 328 cavities under collapse measures, or 65 per cent In comparing the single cavity series with the complete series, it is noted that, since the non-collapse closures were raised from 17 per cent to 26 per cent and the collapse closures from 61 per cent to 65 per cent, the presence of single cavitation more definitely improved the results in the non-collapse group The same trend was noted in the subdivisions based on cavity diameter (chart 4, graph 3)

CHART IV

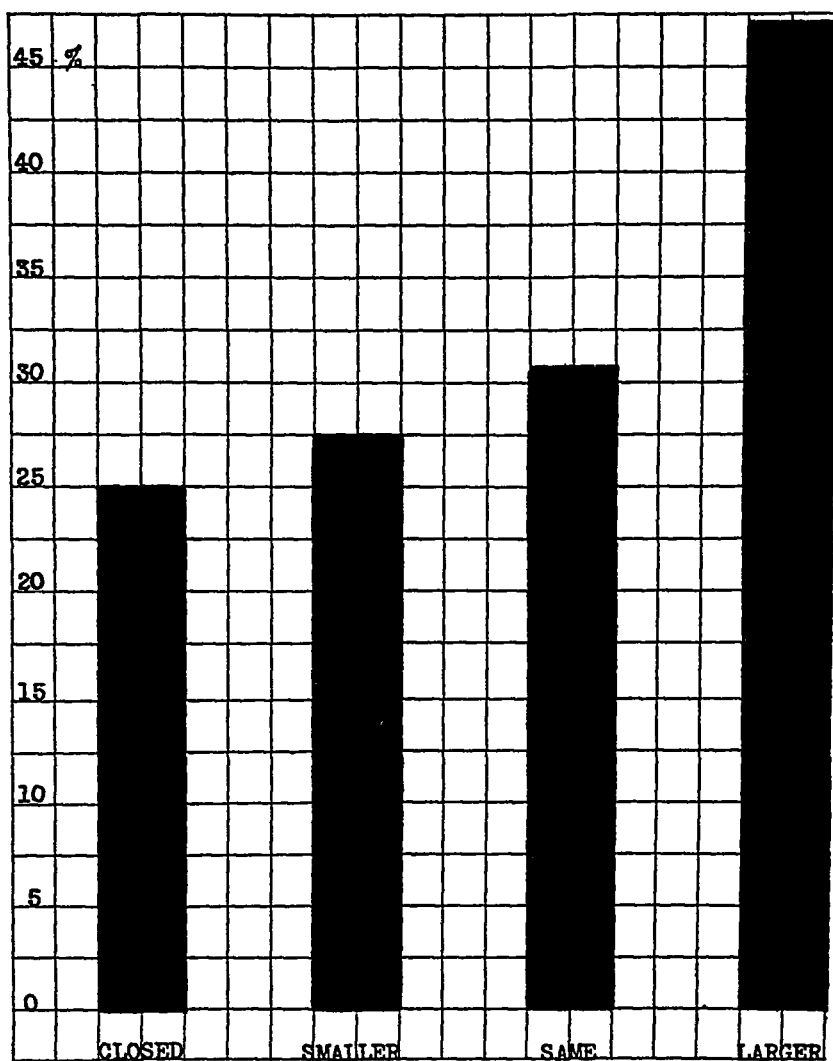
Cavity Closure

A Study of 457 Single Cavity Cases with 573 Therapy Results

Therapy	0-2 cm		2-4 cm		4-6 cm		6-8 cm		8 plus cm		Total	
	No Closed	% Closed	No Closed	% Closed	No Closed	% Closed	No Closed	% Closed	No Closed	% Closed	No Closed	% Closed
Bed rest	0	0	13	46	6	18	2	10	3	8	24	20
Mild activity	4	100	15	44	11	26	8	30	3	15	41	32
Phrenic surgery	1	100	7	53	14	40	3	15	2	5	27	26
Pneumothorax	4	100	27	93	90	89	21	80	21	58	163	83
Thoracoplasty	0	0	1	100	9	100	4	80	12	92	26	93
Non-collapse	4	80	28	45	17	23	10	22	6	11	65	26
Collapse	5	100	35	82	113	78	28	50	35	42	216	65
Total	9	90	63	60	130	59	38	39	41	29	281	49

COMPARISON OF CAVITIES IN THE COLLAPSE AND NON-COLLAPSE GROUPS

Before logical comparisons can be made between various forms of therapy the presence of definitely similar factors must be established The incidence of exudative disease, the average total pulmonary cavitation present, the average number of months necessary for cavity closure, the average duration of each form of therapy, and the average period of observation after cavity closure are all considerations in a study of this type which can influence the results obtained In evaluating these factors it is noted that in the non-collapse series 34 per cent of the cavities were present in cases showing a predominance of exudative disease to 32 per cent in the collapse series The average total pulmonary cavitation present in the non-collapse group was 11 cm whereas in the collapse group it was 8 cm The average number of months required for closure in the non-collapse cavities was 16 and in the cavities under collapse it was 8 Both the non-collapse and the collapse series averaged 24 months on individual therapy measures The non-collapse series was observed for an average of 24 months after closure and the collapse series for a 21 month average (charts 5 to 10)



GRAPH 4 Cavity results in the presence of predominantly exudative disease (see chart 6)

CHART V

Incidence of Predominantly Exudative Disease in Cavity Series

Therapy	0-2 cm		2-4 cm		4-6 cm		6-8 cm		8 plus cm		Total	
	No Exudative	% Exudative	No Exudative	% Exudative	No Exudative	% Exudative	No Exudative	% Exudative	No Exudative	% Exudative	No Exudative	% Exudative
Bed rest	9	32	42	32	47	36	30	38	84	51	212	40
Mild activity	1	7	18	22	7	9	8	16	22	41	56	21
Phrenic surgery	1	33	3	9	18	9	31	24	43	46	27	27
Pneumothorax	4	36	22	31	41	29	16	35	33	44	116	34
Thoracoplasty	0	0	0	0	1	10	1	20	6	43	8	26
Non-collapse	10	25	60	29	54	26	38	30	106	51	268	34
Collapse	5	36	25	25	51	26	26	33	63	44	170	32
Total	15	27	85	27	105	26	64	30	169	46	438	33

CHART VI

Therapy Results in the Presence of Predominantly Exudative Disease

Cavity Size	Closed		Smaller		Same		Larger	
	No Exudative	% Exudative	No Exudative	% Exudative	No Exudative	% Exudative	No Exudative	% Exudative
0-2 cm	6	20	0	0	1	25	8	40
2-4 cm	28	20	11	21	10	25	36	45
4-6 cm	44	24	14	24	9	16	38	36
6-8 cm	14	25	11	21	7	21	32	49
8 plus cm	22	34	37	38	46	46	64	62
Total	114	25	73	28	73	31	178	48

CHART VII

Average Diameter of Total Lung Cavitation in 1333 Individual Cavities

Therapy	0-2 cm	2-4 cm	4-6 cm	6-8 cm	8 plus cm	Total
Bed rest	11 cm	9	11	13	17	15
Mild activity	7	6	8	9	14	9
Phrenic surgery	6	6	7	9	12	8
Pneumothorax	6	7	7	9	14	9
Thoracoplasty		3	6	7	12	9
Non-collapse	10	8	10	12	16	11
Collapse	6	6	7	9	13	8
Total	9	8	8	11	15	11

CHART VIII

Average Months for Cavity Closure

Treatment	0-2 cm	2-4 cm	4-6 cm	6-8 cm	8 plus cm	Total
Bed rest	14	14	20	21	11	16
Mild activity	16	15	14	19	64	18
Phrenic surgery	9	11	14	22	18	13
Pneumothorax	3	6	8	8	12	7
Non-collapse	15	15	17	20	42	17
Phrenic and pneumo-thorax	4	7	8 3	9	12 2	8

CHART IX

Average Months on Each Treatment

Treatment	0-2 cm	2-4 cm	4-6 cm	6-8 cm	8 plus cm	Total
Bed rest	30	20	24	21	24	23
Mild activity	42	24	25	20	35	26
Phrenic surgery	17	21	21	18	22	21
Pneumothorax	23	24	27	27	26	26
Non-collapse	34	21	25	20 4	26	24
Phrenic and pneumo-thorax	22	23	26	24	24	24

CHART X
Average Months Observed After Cavity Closure

Therapy	0-2 cm	2-4 cm	4-6 cm	6-8 cm	8 plus cm	Total
Bed rest	17	25	25	17	30	23
Mild activity	38	22	17	25	41	29
Phrenic surgery	6	24	20	18	16	20
Pneumothorax	35	20	16	26	25	20
Thoracoplasty	—	47	31	12	25	26
Non-collapse	28	24	21	21	36	24
Collapse	30	21	18	24	25	21

There is a marked similarity in the two groups in regard to the proportion of cavities occurring in exudative cases, the average duration of forms of therapy, and the average period of observation after cavity closure. However, the average total pulmonary cavitation is somewhat greater in the non-collapse group, whereas the average number of months necessary for cavity closure is twice as long in the non-collapse series as in the collapse series. Nevertheless the relative similarity of the factors involved in the non-collapse and collapse groups lends added significance to the findings of 17 per cent cavity closure for non-collapse measures and 61 per cent closure for collapse therapy.

CASES WITH ALL CAVITIES CLOSED

Closure of all pulmonary cavities was obtained in 331 of the 750 cases used in this study. There were 457 cases with single cavitation and 293 cases presenting two or more cavities. Closure of all pulmonary cavities was obtained in 60 per cent of the single cavity cases and in 17 per cent of the multiple cavity cases. The total percentage of cases with all cavities closed was 44.

SUMMARY

A study of 750 cases of cavernous pulmonary tuberculosis with 1097 individual cavities has been presented. Classification of cases as to extent of disease showed that 95 per cent were far advanced. Roentgen changes in individual cavities were noted for patients on bed rest, mild activity, phrenic nerve surgery, pneumothorax, thoracoplasty, and on combinations of these measures. Comparisons were made not only for each form of therapy but also for cavities of definite size under these forms of therapy. The results of non-collapse and collapse measures were tabulated and studies made to show the similarity of the cavities listed under these two major forms of therapy. Finally, the cases with complete cavity closure were presented.

CONCLUSIONS

1 Successful therapeutic results are inversely proportional to the diameter of total pulmonary cavitation, the diameter of the individual cavity, and the preponderance of exudative disease

2 Individual cavities close more readily in single cavity cases than in multiple cavity cases

3 Collapse measures are three times as effective as non-collapse measures in closing individual cavities

4 In single-cavity cases collapse measures are twice as effective as non-collapse measures in closing the cavity

5 The average time required for cavity closure is half as long with collapse therapy as with non-collapse therapy

6 Closure of all cavities occurs four times as frequently with localized cavitation as with disseminated cavitation

REFERENCE

- 1 SALKIN, DAVID, and CADDEN, A V Rest and collapse in pulmonary tuberculosis, Read before the American Society for Thoracic Surgeons in June, 1940

IDIOPATHIC CARDIAC ENLARGEMENT OCCURRING IN INFANTS AND CHILDREN *

By J MARSHALL NEELY, M D , F A C P , *Lincoln, Nebraska*

CONGENITAL idiopathic cardiac hypertrophy is a term which has been used to designate cardiac enlargement occurring in infants and young children with no demonstrable etiology. As more attention is given to this group of cases it becomes apparent that those which are truly idiopathic constitute a small minority. S Van Creveld² and others have shown that many cases of cardiac enlargement thought to be idiopathic are Von Gierke's disease, or "hepatomegalia glycogenica," in which there is glycogen infiltration of the heart, liver, and kidneys. Cardiac enlargement has also been shown to occur in the primary anemias of childhood, particularly in sickle cell anemia. According to Kugel and Stoloff⁷ some have attempted to explain cardiac hypertrophy and dilatation on the basis of so-called status thymico-lymphaticus. Kugel⁹ divides cardiac enlargement of infancy into eight main groups: congenital defects, infections, anemias of long standing, non-suppurative myocardial degeneration, metabolic disorders, hypertension, tumors, and finally the unclassified. Vitamin B₁ deficiency has recently¹⁸ been shown to play an important rôle in the production of cardiac hypertrophy of adults and its importance in infants must be considered.

The material upon which this communication is based is supplied from the clinical records, roentgen-ray films, and autopsy material from three infants.

CASE REPORTS

Case 1 A male infant 25 days of age was admitted to the hospital because of difficult feeding, crying, and cyanosis. At the time of birth nothing unusual was noted and symptoms developed about 10 days before admission to the hospital. Rapid respiration and cyanosis were observed the day of admission to the hospital. Examination disclosed fever, grunting respiration, restlessness, sunken fontanel, and circumoral cyanosis. Respirations were about 100 per minute and breath sounds were harsh, particularly over both bases. No dullness could be elicited in either lung field. There was clinical evidence of an enlarged heart both by percussion and roentgen study. The pulse rate was estimated at 290. A cardiac murmur was heard over the precordium. The liver edge was at the umbilicus and the extremities were not remarkable. The patient died quite suddenly on the fourth hospital day. During the hospital stay the temperature varied from 100 to 103° F.

Postmortem Findings There was slight pleural effusion in the pleural cavity. Both lungs were voluminous and firm in consistency. The heart weighed 80 gm and there were no congenital anomalies evident. There was enlargement of the liver and to a lesser extent the spleen. Microscopically there was some fragmentation of the muscle in the myocardium and small areas of degeneration. There was also a slight

* Received for publication February 26, 1940

From the Department of Radiology, Lincoln General Hospital



FIG 1 A single A P film showing cardiac enlargement and decreased aeration throughout both lung fields (Case 1)

diffuse lymphocytic infiltration seen throughout the myocardium. Chronic passive congestion was present in the liver and kidneys. Sections of the lungs showed an advanced interstitial pneumonitis with thickening of the alveolar septae and lymphocytic infiltration. There was also evidence of collagen formation in the septae. Practically no capillaries could be found in the alveolar septa. The alveolar spaces were decreased in size or obliterated.

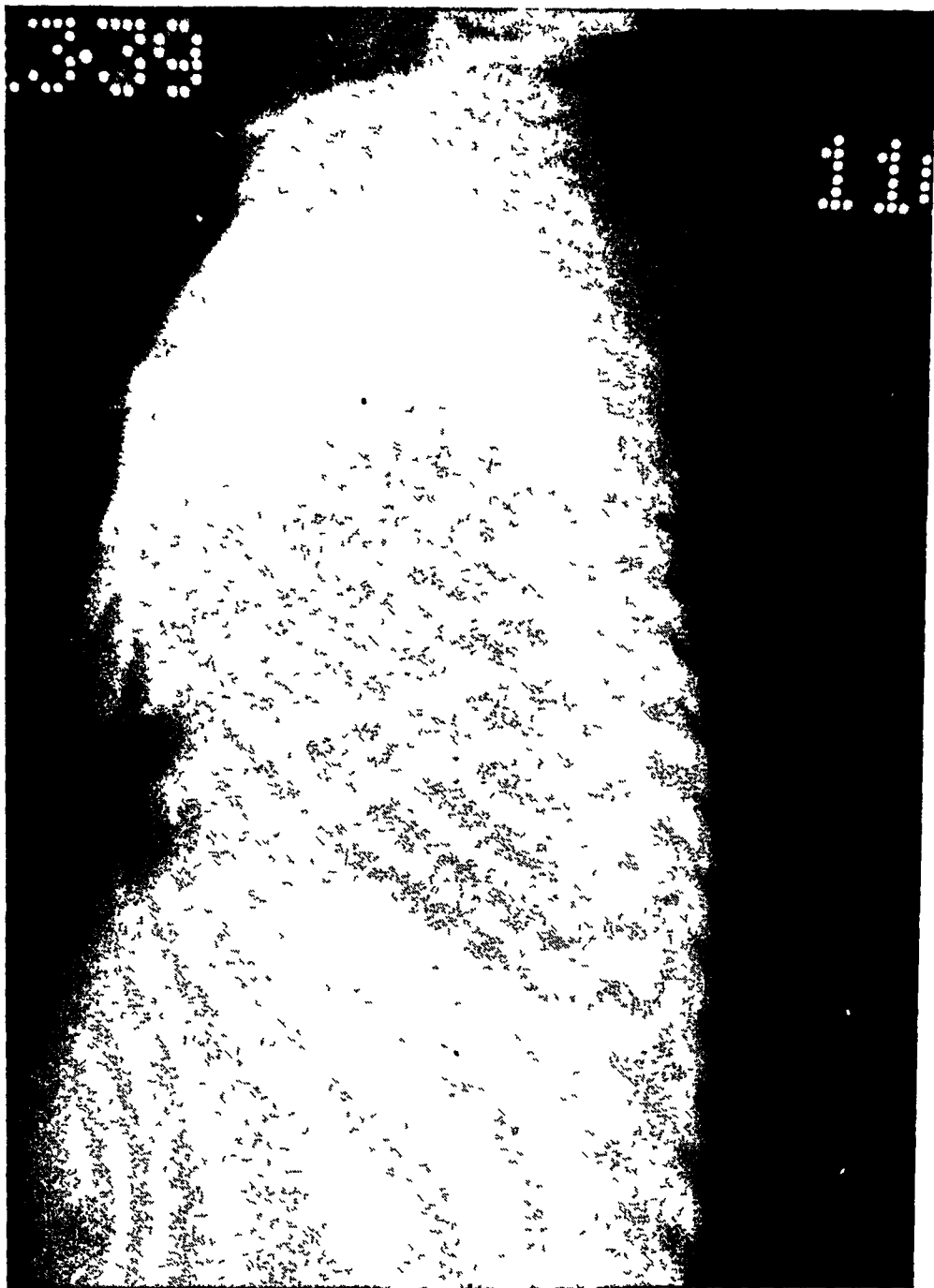


FIG 2 In the lateral position there is no evidence of displacement of the trachea and the mottling is again seen in the lung fields

Case 2 A white female infant, age 11 months, was perfectly well until the day of her death. No definite history of illness could be elicited from the parents. Death occurred quite suddenly while she was taking her bottle.

Postmortem Findings There was marked cardiac enlargement without evidence of congenital defect. Hypertrophy was most pronounced in the right ventricle and there was dilatation of the right atrium. The left ventricle was about normal in size.

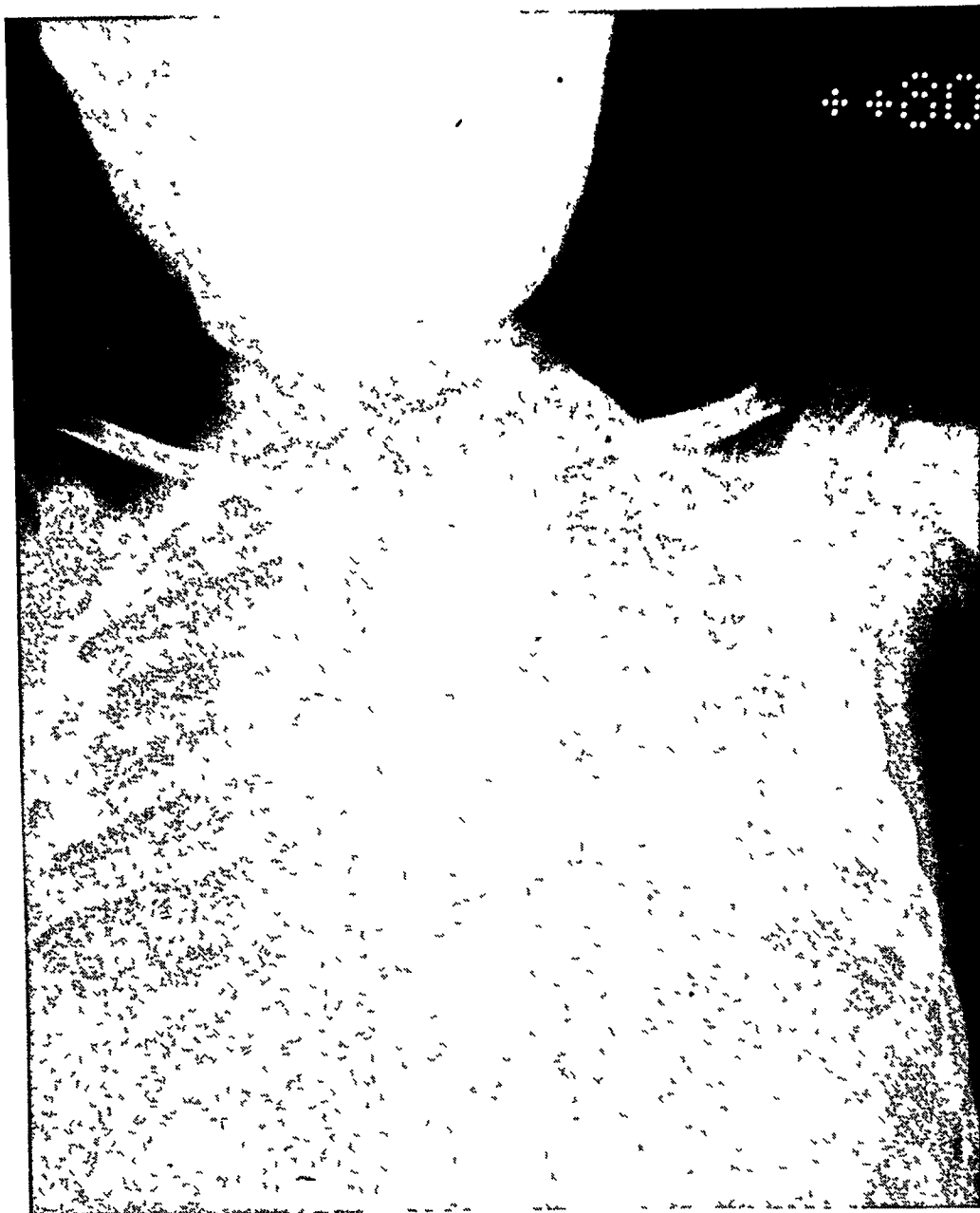


FIG 3 A single A P film of the chest showing marked cardiac enlargement with some displacement of the trachea to the right Configuration particularly suggests right heart enlargement (Case 3)

Both lungs were normal in size though there was less aeration than normal The cut surfaces appeared somewhat meaty

Microscopically the myocardium showed small areas of fragmentation and a slight polyblastic cellular infiltration The lungs showed tremendous thickening of the alveolar walls with proliferation of alveolar phagocytes and, as demonstrated by means of Masson's trichrome stain, definite collagen formation Very few capillaries were found There were small areas of emphysema present

Case 3 A white male child, age three years, was admitted to the hospital June 9, 1935, complaining of dyspnea, weakness, orthopnea and cough Dyspnea was first noted about four weeks before admission and became much more noticeable about one week before admission Associated with these symptoms was cough, non-productive



FIG 4 Section of myocardium showing fragmentation of the muscle fibrils Note mitotic figure near top of illustration

in character, which became worse when the patient was lying down. Examination showed slight cyanosis, and labored rapid respiration. The left side of the chest was larger than the right. There were harsh breath sounds, and bronchial breathing could be heard below the left scapula. There was tremendous enlargement of the heart which was very rapid. No murmurs were heard. No fluid or masses could be found in the abdomen though there was enlargement of the liver and edema of the lower

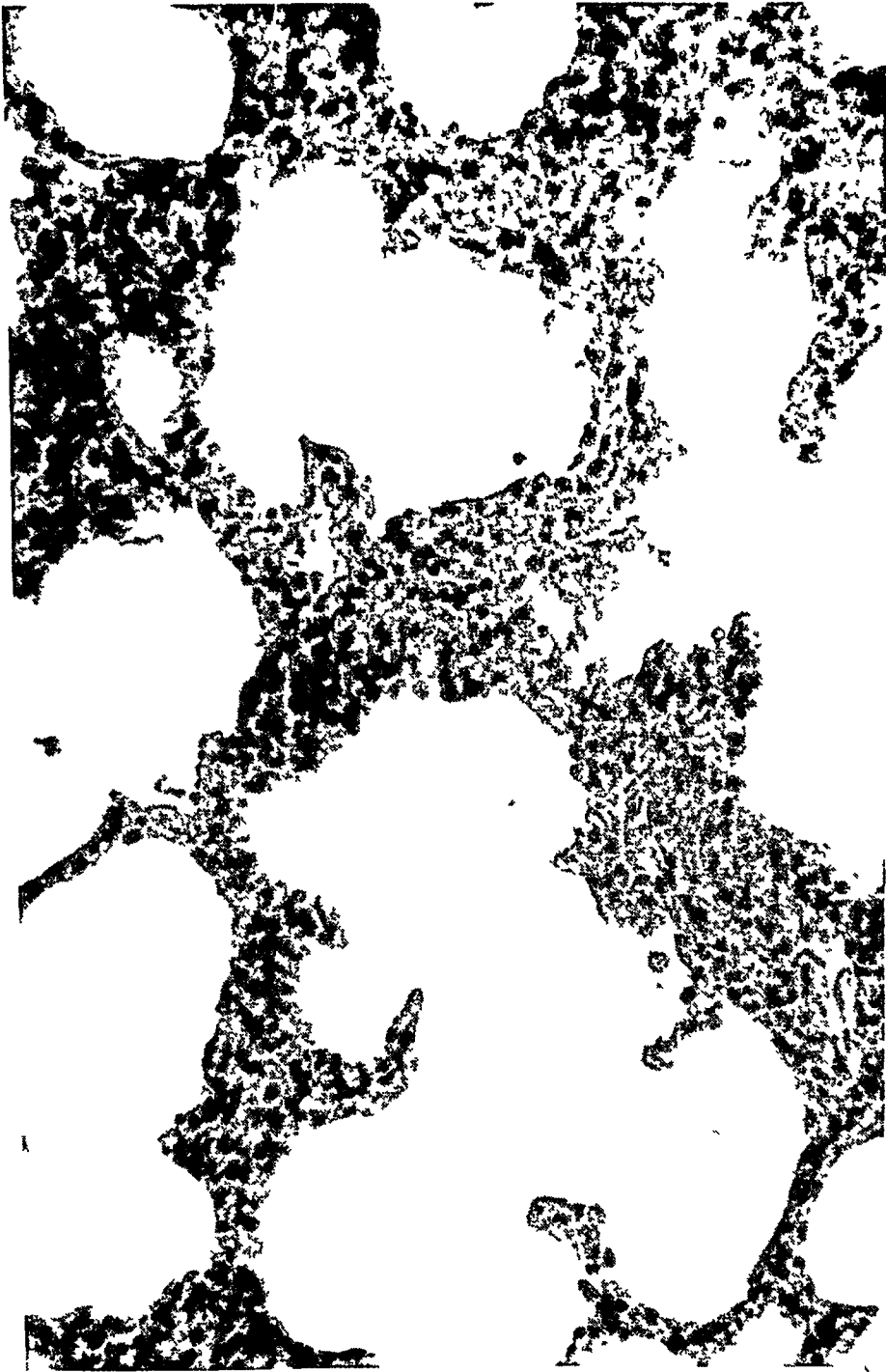


FIG 5 Section of lung illustrating marked interstitial proliferation of alveolar septa with polyblastic cellular infiltration Note absence of alveolar capillaries (Case 1)

extremities A general anasarca developed terminally and death occurred on August 3, 1935

Postmortem Findings There was ascites and bilateral pleural effusion The liver and spleen were enlarged due to passive congestion The heart was markedly enlarged There were no congenital anomalies present There was marked right ventricular hypertrophy and the right atrium was so dilated that its wall was almost parchment thin There was also dilatation of the pulmonary artery which measured



FIG 6 Higher power view of same lung showing marked proliferation of histocytes and collagen formation (Case 1)

3 cm at the base. Some small atheromatous plaques were seen in the intima of the pulmonary artery. The left lung was smaller than the right. Both were heavier than normal and small grayish areas were seen beneath the pleura. On cut section there was evidence of emphysema though the cut surface was quite firm in consistency. Microscopically many lung sections showed an advanced chronic pulmonary emphysema, in some areas a definite interstitial pneumonitis existed. The myocardium



FIG 7 Section of bronchial wall showing edema and cellular infiltration

showed hypertrophy of the muscle fibers and very small patches of fibrosis. There was also marked passive congestion of the liver, kidneys, and spleen.

While these three clinical courses vary considerably there are certain symptoms and findings common to all. Dyspnea, cyanosis, rapid pulse and cardiac enlargement were present in each, though in the child who died

suddenly, cardiac enlargement was not discovered until after death. The length of illness varied from sudden death to three months. According to Mahon⁶ the average age incidence in idiopathic cardiac hypertrophy is 14 months. The onset is usually rapid and the three cardinal findings are cyanosis, dyspnea and tachycardia. Anemia and fever may be present and edema and heart murmurs are occasionally found. The few electrocardiograms done in those cases reported in the literature show shallow T-waves, low voltage in all leads, and a tendency to left ventricular preponderance. There is often prolongation of the PR interval. Terminally, liver enlargement and edema commonly occur.

According to Kugel⁹ roentgenograms demonstrate marked cardiac enlargement in all diameters with either right or left preponderance. Many times it is impossible to eliminate the presence of congenital heart disease roentgenographically. Roentgen examination was possible in the 25 day-old baby (Case 1) and in the 3-year-old boy (Case 3). In the first case (figure 1) films show marked cardiac enlargement in all diameters apparently involving both right and left heart though the right seems to be predominant. The cardiac shadow is not sharply outlined and there is fine mottling and decreased aeration throughout both lung fields. The trachea is in normal position in both antero-posterior and lateral projections (figure 2). There is no roentgen-ray evidence of emphysema. Antero-posterior (figure 3) chest films of the 3-year-old boy show marked cardiac enlargement with slight displacement of the trachea to the right. Here, too, both the right and left heart are enlarged, though in this case the lung fields are hyperaerated. In one of the films made just prior to this there is spontaneous pneumothorax on the left. The costal spaces are widened and there is flaring of the anterior ribs. The heart fills most of the chest and the conus pulmonalis is prominent. The terminal appearance of pneumothorax was due to rupture of a pleural bleb which developed as a result of emphysema.

The autopsy findings in these three cases are so similar that they may well be described together. In each there was marked cardiac hypertrophy without congenital anomaly or valve defect. Though hypertrophy was present in both right and left heart it was most marked on the right in all three instances. Chronic passive congestion of the liver was also a constant finding and in the case of the 3-year-old boy (Case 3) there was ascites and pleural effusion. In the other two autopsies the lungs were heavy, crepitation was diminished or absent, the cut surface was liver-like in consistency, yellowish-gray and edematous. Small grayish areas could be made out beneath the pleural surface in these two cases. The boy who lived three months after onset (Case 3) presented lungs which were voluminous and emphysematous, but the cut surface was firm in consistency. Small pleural blebs were encountered on the left. The thymus was large though not unusually so in the 11-month-old infant (Case 2) who died suddenly. In the two older children the thymus was atrophic.



FIG 8 High power view of alveolar septum showing marked proliferation of alveolar histocytes and collagen formation No capillaries are visible

Sections of myocardium in each instance show fragmentation and degeneration of muscle fibers with occasional small areas of lymphocytic infiltration. There is some loss of cross striations in selected areas. Indigo-carmin stains were negative for glycogen in one instance. This technique was not possible in the other two due to formalin fixation of tissue. There

was some endocardial thickening in both right and left ventricles, most marked on the right. Moderate perivascular fibrosis of the terminal branches of the coronary arteries was evident. The terminal branches of the coronaries were not remarkable.

• The histological changes noted in the myocardium in all three hearts are quite similar. Though these changes conform in every respect to those described in cases of congenital idiopathic cardiac hypertrophy, there is little reason to believe that they represent other causes. Mitotic figures were seen in two of the hearts, but it has been shown⁸ that this finding is not uncommon in cardiac hypertrophy in infants up to 20 months of age regardless of the cause of the hypertrophy. No mitotic figures could be found in the myocardium of the 3-year-old child (Case 3). The perivascular increase in collagen and patches of lymphocytic infiltration as well as fragmentation are changes not uncommon in myocardial hypertrophy occurring in nephritis, congenital heart disease or other primary diseases remote from the heart.

Little attention has been given to the histologic changes in the lungs in cardiac hypertrophy occurring in infants. Some^{7,8} have mentioned atelectasis though little import has been attached to it. Most of the lung changes have been attributed to primary cardiac pathology. McCordock and Muckenfuss¹⁴ have presented evidence that interstitial pneumonitis occurs in two forms depending upon the concentration of virus. These conclusions are based on experimental and clinical observation. If experimental animals are given concentrated doses of virus there is an explosive type of histologic reaction with fibrin deposits in the alveolar spaces and necrosis of the wall. If given in more dilute form the histologic response within the alveoli is proliferative. Here the septa become thickened by proliferating histocytes, there is thickening of the adventitia of the vessels and mononuclear cellular infiltration of the walls of the bronchioles and arteries. The lining cells of the alveoli also proliferate. In the first type of reaction death occurs early due to what is usually termed "hemorrhagic virus pneumonia." In the proliferative type the process may resolve after a period of several weeks or may go on to chronicity.

Sprunt, Martin and McDearman¹⁵ described much the same type of histologic reaction when they injected Bordet-Gengou bacilli intratracheally in the monkey and rabbit. Sections of the lung made soon after the injection showed alveoli filled with hemosiderin containing macrophages, and sections made 14 days after inoculation showed beginning proliferation of interstitial tissue. They found that heat-killed cultures produced a material which, by acting as a foreign body, produced lesions in the lungs similar to that seen with the virus itself. They showed that the avirulent form could also cause interstitial pneumonitis.

Although there has been considerable clinical and experimental observation on the pulmonary histology of virus disease in its early and fatal stages, little attention has been directed toward the lungs in those cases which re-

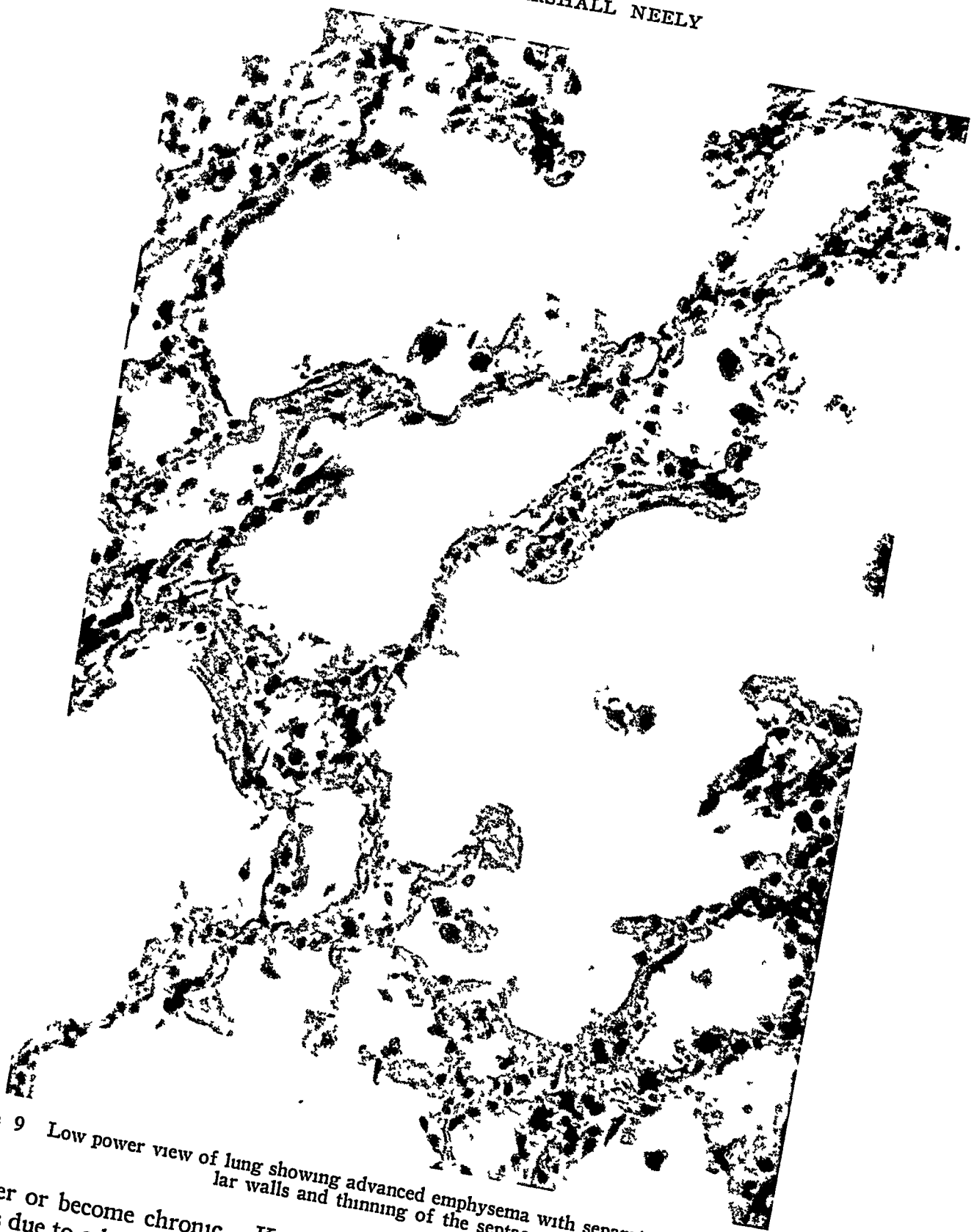


FIG 9 Low power view of lung showing advanced emphysema with separation of the alveolar walls and thinning of the septae

cover or become chronic
nitis due to oil aspiration
filtrable virus

Kano-Ikeda¹⁶ has described interstitial pneumo-
The histology is very similar to that produced by

Parker and Weiss¹⁷ have described in detail the histologic changes taking place in pulmonary alveoli in far advanced mitral stenosis. Here, the first change is thickening of the capillary basement membrane which is later followed by edema, interstitial proliferation of cells and later in the most advanced stages by thickening of the alveolar basement membrane. They also describe thickening of the intima in branches of the pulmonary artery. In mitral stenosis there is marked increase in the number of alveolar capillaries which become coiled and dilated. They also point out that in cases of chronic pulmonary emphysema and repeated attacks of pneumonitis the same responsible factors are apt to coexist and hence pulmonary hypertension and arteriolar sclerosis are apt to occur. Snow and Cassasa¹⁸ believe that emphysema commonly coexists with influenza and bronchopneumonia in infants. They state emphysema may be demonstrated in almost all infants with acute respiratory infection. They also think emphysema is obstructive and not compensatory. Shanks, Kerley and Twining¹⁹ state that cardiac enlargement occurs in 40 per cent of cases of chronic emphysema with involvement of the right ventricle predominating, and that there is also enlargement of the conus pulmonalis in about half of these cases. The pulmonary changes in all of the three examples of cardiac enlargement forming the basis of this report are responsible for the cardiac hypertrophy and death. Many sections of these lungs were stained with hematoxylin and eosin, and Masson's trichrome stain. In the two cases with short clinical courses (Cases 11 and 12) the histologic changes are those of marked interstitial proliferation of alveolar phagocytes with thickening of alveolar walls. In most areas there is complete obliteration of alveolar spaces. In contrast to the picture described by Parker and Weiss¹⁷ interalveolar capillaries are few in number and there is no evidence of thickening of the basement membrane. In the sections stained with Masson's trichrome methods there is definite evidence of laying down of collagen in the alveolar walls. Alveolar phagocytes are encountered in the few alveolar spaces which remain. Lymphocytic infiltration is seen throughout all of the thickened alveolar walls. Lymphocytic and monocytic infiltration is also found in the bronchial walls and in some areas there has been complete displacement of the alveolar walls by adult collagen. Most of the terminal arteries show thickening of adventitia and media. In an occasional small artery there is complete obliteration of the lumen by an old organized thrombus undergoing canalization. Sections made near the pleura show dilatation of vessels and diapedesis of red cells which must be interpreted as an attempt on the part of the bronchial circulation to compensate for the obstructive process taking place in the pulmonary circulation.

In the case of the 3-year-old boy (Case 3) whose clinical course was much more prolonged, the histologic picture is characteristic of chronic pulmonary emphysema. In many areas, however, there is evidence of preëxisting chronic interstitial pneumonitis. The relationship of interstitial pneumonitis

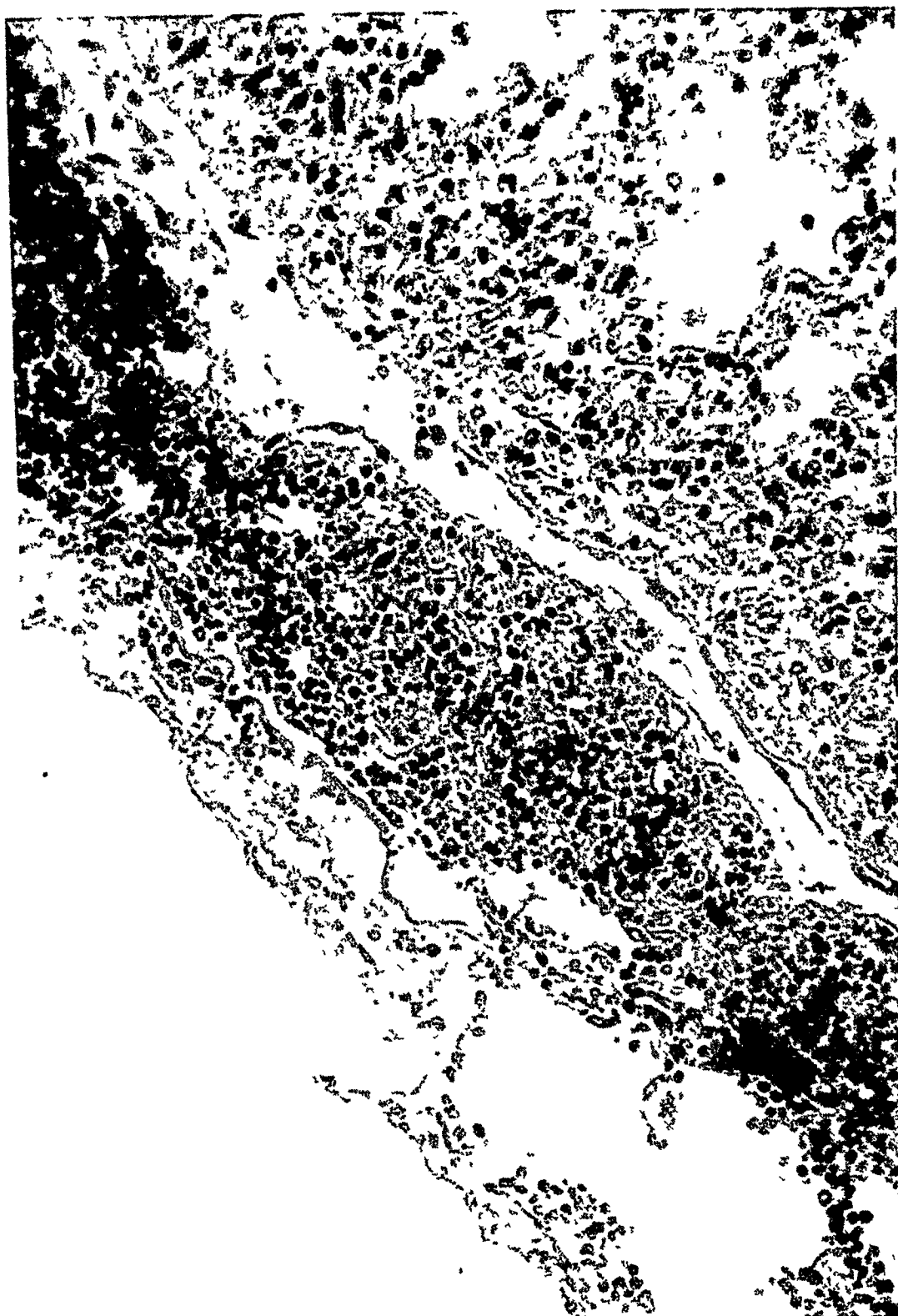


FIG 10 Section including pleura showing marked dilatation and congestion of subpleural vascular supply indicating compensatory part taken by the bronchial circulation

and pulmonary emphysema is clearly demonstrated. The general picture of the areas in these sections where interstitial pneumonitis persists is essentially the same as in the above described sections except that there is much more

collagen within the alveolar septa. In the emphysematous areas the capillaries are totally obliterated by collagen and remain as functionless as in the areas of cellular proliferation.

The effect of these changes on the right heart is essentially the same as those produced in advanced mitral stenosis in which there is elevation of pulmonary arterial pressure due to quite similar histologic changes in the alveolar walls and terminal pulmonary arteries. That these changes do not represent the result of long standing chronic passive congestion is evidenced by the presence of diffuse infiltration with lymphocytes and mononuclear cells and by the absence of proliferation and dilating alveolar capillaries. These capillaries in interstitial pneumonitis are closed or crowded out by the proliferating interstitial cells. That such alveolar changes produce increased pulmonary arterial pressure, however, is evidenced by the changes in the pulmonary arterioles, and the compensatory congestion and dilatation of the bronchial circulation beneath the pleura.

Attention has recently been directed toward the roentgen changes in acute and chronic interstitial pneumonitis. Reimann²¹ recently described eight cases which he considered due to virus infection. Roentgenograms showed mottled increased density throughout both lung fields. Smiley and Showacre²⁰ described acute interstitial pneumonitis occurring in students at Cornell University. They pointed out that no roentgen-ray change is seen in the acute form until 48 to 72 hours have elapsed. They believe infection spreads from the hilum region outward. They also observed that the infection may clear up in from one to two weeks or may last up to three months. Snow and Cassasa¹⁸ have emphasized the importance of emphysema, particularly where interstitial pneumonitis exists.

In those infants in whom cardiac enlargement exists it is important that careful attention be given the lung fields. If cardiac enlargement has occurred on the basis of interstitial pneumonitis it is likely that the pulmonary lesion has been present for some time. However, as pointed out by Parker and Weiss,¹⁷ alveolar and arterial changes may take place in a relatively short period of time. Fine mottled increased density throughout both lung fields in films showing cardiac enlargement in infants will often be interpreted as chronic passive congestion, and unless observed over a considerable period of time with serial films, there is probably no definite method of making an accurate differential diagnosis between these two entities. Persistent fine mottling despite therapeutic measures for cardiac decompensation should direct one's attention to the possibility of chronic interstitial pneumonitis and in turn must be considered as a possible cause of cardiac hypertrophy.

CONCLUSION

Clinical and autopsy findings in three cases of cardiac enlargement in infants have been described. Evidence is presented to support the contention that, while the gross and microscopic changes in the heart are in each

instance consistent with the diagnosis of idiopathic cardiac hypertrophy, the primary cause of these changes is chronic interstitial pneumonitis with secondary cardiac hypertrophy. It is suggested that the rapidly dwindling group known as idiopathic cardiac hypertrophy will decrease still further if more attention is given the lungs clinically and at autopsy. Chronic pulmonary emphysema as the compensatory change in interstitial pneumonitis adds to the load placed on the right heart. Cardiac enlargement occurring in infants may be due to many and various causes. If such an entity as congenital idiopathic cardiac hypertrophy exists it must be so classified only after due consideration is given to all the possible causes.

BIBLIOGRAPHY

- 1 DAMMIN, G J, and MOORE, R A Cardiac muscle in idiopathic hypertrophy of infancy, *Arch Path*, 1929, xxvii, 122-127
- 2 CREVELD, S VAN Glycogen disease, *Medicine*, 1939, xviii, 1-128
- 3 POWERS, C F, and Lecompte, P M Congenital idiopathic cardiac hypertrophy, *Case, Jr Pediat*, 1939, xiii, 760-771
- 4 MACMAHON, H E Hypertrophy of heart in infants, *Am Jr Dis Child*, 1938, lv, 93-99
- 5 MAHON, G S Idiopathic hypertrophy with endocardial fibrosis, two cases, *Am Heart Jr*, 1936, xii, 608-617
- 6 STOLOFF, E G So-called idiopathic enlargement of the heart in infancy and childhood, *Am Jr Dis Child*, 1928, xxxvi, 1204
- 7 KUGEL, M A, and STOLOFF, E G Dilatation and hypertrophy of the heart in infants and young children, *Am Jr Dis Child*, 1933, xlv, 828
- 8 LEVINE, H D Cardiac hypertrophy in infancy, *Am Jr Dis Child*, 1934, xlviii, 1072
- 9 KUGEL, M A Enlargement of the heart in infants and young children, *Am Heart Jr*, 1939, xvii, 602-615
- 10 YATER, W M, and HANSMANN, G H Sickle-cell anemia, a new cause of cor pulmonale, *Am Jr Med Sci*, 1936, cxc, 474
- 11 MACMAHON, E E Hyperplasia and regeneration of the myocardium in infants and in children, *Am Jr Path*, 1937, xiii, 845
- 12 SIMMONDS, J Ueber congenitale primare Herzhypertrophie, *Munchen med Wchnschr*, 1899, xlv, 108
- 13 WEISS, SOMA, and WILKINS, ROBERT The nature of cardiovascular disturbances in deficiency states (beriberi), *ANN INT MED*, 1937, xi, 104-146
- 14 MCCORDOCK, H A, and MUCKENFUSS, R S The similarity of virus pneumonia in animals to epidemic influenza and interstitial bronchopneumonia in man, *Am Jr Path*, 1933, ix, 221-252
- 15 SPRUNT, DOUGLAS H, MARTIN, DONALD S, and McDEARMAN, SARA Results of intratracheal injection of the Bordet-Gengou bacillus in the monkey and rabbit, *Jr Exper Med*, 1938, lxxvii, 309
- 16 IKEDA, K Oil aspiration pneumonia (lipoid pneumonia), *Am Jr Dis Child*, 1935, xlix, 985
- 17 PARKER, FREDERIC, and WEISS, SOMA The nature and significance of the structural changes in the lungs in mitral stenosis, *Am Jr Path*, 1936, xi, 573
- 18 SNOW, WILLIAM, and CASSASA, C S B Obstructive emphysema and atelectasis in acute respiratory disease of infants, *Am Jr Roentgenol*, 1937, xxxvii, 217-220
- 19 SHANKS, S C, KERLEY, P, and TWINING, E W A textbook of x-ray diagnosis, 34
- 20 SMILEY, D F, SHOWACRE, E C, LEE, W F, and FERRIS, H W Acute interstitial pneumonitis a new disease entity, *Jr Am Med Assoc*, 1939, cxii, 1901
- 21 REIMANN, HOBART A An acute infection of the respiratory tract with atypical pneumonia, *Jr Am Med Assoc*, 1938, cxi, 2377-2384

CASE REPORTS

COLD ALLERGY REPORT OF AN UNUSUAL CASE*

By WALLACE M YATER, M D , F A C P , and EDWARD W NICKLAS, M D ,
Washington, D C

Cold allergy has been known since 1866, when Bourden¹ described urticaria and syncope due apparently to cold. However, in 1872 Blachez² gave the first classical description of urticaria from cold. Since then several other writers have reported cases of this form of allergy. Since 1924 Duke³ has written voluminously on this subject, describing various forms of physical allergy, which he found to be not uncommon. He suggested the possibility that a histamine-like substance might be liberated locally and be responsible in some instances. Lewis⁴ later showed the probable existence of such a substance. In 1929 Horton and Brown⁵ reported a study of six cases of cold allergy in which attacks of syncope resulted from exposure of the skin to cold. They showed that if a tourniquet were applied to an extremity proximal to the chilled area the reaction would not occur. In 1936 Horton, Brown and Roth⁶ published an outstanding contribution to this subject.

Duke's original method of testing for cold allergy consisted of either simply rubbing the skin with a block of ice or of alternating this with exposure to heat in order to produce a sudden change in temperature. He found that application of the opposite excitant quickly terminated the reaction (urticaria, asthma, sneezing, etc). Horton, Brown and Roth placed the patient's hand and part of the forearm in water at about 9° C (48° F) for six minutes. A positive reaction consisted in the appearance three to six minutes later of local pallor which changed to redness, slight edema and an increase in local temperature. Sometimes a constitutional reaction followed with fall in blood pressure, rise in pulse rate, vertigo and even syncope. These manifestations were quickly counteracted by dipping the patient's hand in warm water or by applying a tourniquet above the elbow. Reenforcement of the reaction could be obtained by repeating the test while a tourniquet was applied to the arm above the elbow and then released. The subsequent reaction appeared sooner, was more severe and lasted as much as three times longer. The disappearance of the reaction occurred in six to eight minutes after its onset following the simple immersion of the hand and forearm in cold water.

The reactions to cold are thus seen to consist of contact reactions and reflex-like reactions (Duke). Syncopal reactions may be responsible for drowning (Horton, Brown and Roth). It has been suggested that chilblains may be due to cold allergy. Apparently, in rare instances, sensitization to cold may be passively transferred.

Treatment of uncomplicated cold allergy is often effective. For the attack the application of heat often dissipates the symptoms. Cure may be accom-

*Received for publication June 7, 1940

plished in a few weeks by two methods. A hand is immersed in cold water for six minutes twice daily, the temperature of the water gradually being decreased from 65° F to 45° F as tolerance develops. The second method of treatment consists of injecting 0.1 mg of histamine subcutaneously twice daily.

An excellent general summary of the subject of physical allergy is given by Vaughan.⁷

The following case is one of complicated cold allergy different from any thus far reported.

CASE REPORT

Mr G W C, a 53-year-old white married salesman, consulted one of us (E W N) first in October 1935 complaining of "sciatic neuritis." He had had a similar attack in 1929 which lasted for three months in spite of the extraction of an abscessed tooth. Subsequently he had recurrent attacks which were not relieved by the extraction of other teeth. The worst attack occurred in 1932, this cleared up after a rectal abscess was discovered and incised. An orthopedist pronounced the "sciatic neuritis" sacroiliac strain. The attack in 1935 ceased after strapping of the pelvis with adhesive tape. Earlier illnesses were typhoid fever in 1892 and malaria in 1910 and 1920. Admission to the army had been refused in 1917 because of albuminuria, but life insurance had been granted in 1914 and was allowed again in 1934. For several years he had had intense bitemporal headaches not associated with nausea or vomiting.

In 1935 he stated that he had been troubled somewhat with hives which he had observed were worse when he ate something cold or exposed himself to cold atmospheres. In the summer of 1935 he had discovered that he could not go swimming without provoking an attack of hives.

In June 1936 his "sciatica" recurred more intensely and was accompanied by numbness and tingling of the right foot and dragging of this foot during walking. There was also numbness of the right hand and occasional difficulty in holding a pencil. This condition gradually subsided.

In September 1937 he complained of intense urticaria induced by cold and cold objects. For instance, sitting in an air-cooled theater first caused blueness of the left ear. Later, red blotches appeared on the feet and ankles, subsequently spreading to the thighs and waist. Still later the tongue, lips, nose and ears swelled up after eating ice cream or drinking cold water. From December 1937 on, the lesions on the ears and ankles appeared frequently with painful swelling and subcutaneous hemorrhages particularly into the helices of the ears during the acute phase. Blood cell counts were essentially normal. Between attacks purplish discoloration and pigmentation of the ankles was present.

In March 1938 he was examined at the Johns Hopkins Diagnostic Clinic. The following diagnoses were made: Chronic urticaria, purpura, hypersensitiveness to cold, low-back strain, benign prostatic hypertrophy, and external and internal hemorrhoids. It was noted that when a piece of ice was held next to the skin for 15 to 30 seconds a typical hive developed at the site of contact within 2 to 4 minutes. Attempts at passive transfer were negative. Dr Leslie N Gay suggested the use of histaminase or exposure of the hands to cold water. An interesting feature of these examinations was the urinalysis, which showed three plus albumin, numerous red blood cells and less numerous white blood cells. All other laboratory tests gave essentially normal results, including blood cell counts, platelet count, bleeding time and coagulation time.

Eight injections of histamine were given but were discontinued because of pronounced flushing of the skin and the formation of huge wheals at the sites of injection.

Purpuric spots similar to those on the ears began to appear more frequently on the ankles and remained for weeks as small, painful areas somewhat resembling areas of superficial gangrene. A purplish macular eruption extended from the ankles to the thighs and occasionally around the waist. Later it temporarily involved the hands, which on the slightest exposure to cold air became dusky and covered with painful hemorrhagic areas. In April 1938 the administration of histaminase was begun and continued for two months without improvement. Other forms of treatment employed later were subcutaneous injections of vitamin C, intravenous injections of typhoid vaccine and intravenous injections of 2 per cent salt solution, but the disease progressed and the legs became swollen and painful. In November 1939 the urine became scanty and smoky and was voided frequently and painfully. It contained four plus albumin and many red and white blood cells. Some specimens showed gross blood. This



FIG 1 Purpuric lesions of the helix of the ear

condition subsided in a month. A course of injections of snake venom was given with questionable improvement.

By March 1939 the disturbance had become so bad that even in warm weather the manifestations persisted, and the patient went about most of the time with ear muffs, gloves and woolen underwear and socks. Colder weather would cause an exacerbation, bringing on an "attack." The patient described this as follows: The ears would begin to itch and soon a throbbing pain would develop. Codeine might give some relief. The hands, feet and ankles quickly became swollen also, and the feet would feel numb. All affected parts would then quickly become bluish and later almost black. The swelling would subside in 12 to 18 hours, and scales would form on the helices of the ears in a few days (figure 1). Before the effects of one "attack" were over, another "attack" would occur. "Attacks" occurred about every 8 to 10 days. The urticaria had become much less prominent. The patient had lost about 13 pounds during the preceding years on account of the suffering. Sleep was restful but interrupted three or four times by urination because of the prostatic obstruction.

Examination at this time was not remarkable except for the appearance of the affected parts. The ears, fingers and feet were moderately swollen and there were discrete punctate hemorrhagic areas on the extremities, most numerous on the feet and ankles, but noticeable up to the thighs. The helices of the ears showed painful bluish-black hemorrhagic lesions and scales or crusts. Some of the lesions on the feet were superficially ulcerated. It was noticed that after the blood pressure reading had been made a wheal developed within 2 to 4 minutes at the site of pressure of the cool rim of the stethoscope. A small cube of ice was held against the skin of the chest and arms at various sites for from 10 to 20 seconds, and wheals developed at these sites in

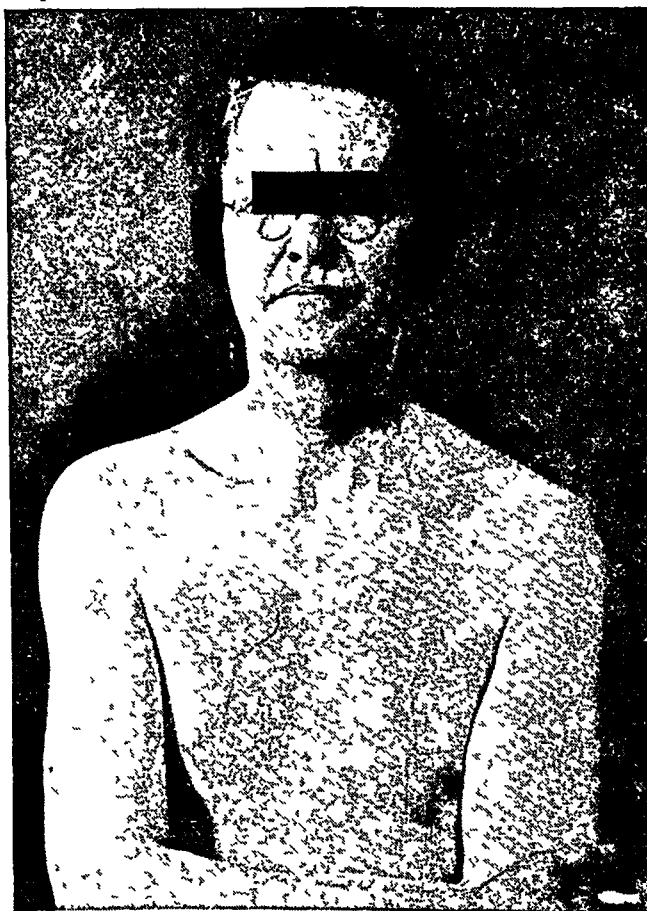


FIG 2 Urticarial wheals on the trunk and arms produced by the application of cubes of ice (Note the ear muffs almost constantly worn)

from 2 to 4 minutes (figure 2). Where the water melted and ran down on the skin wheals also appeared. The cold-pressor test of Hines and Brown was performed. The basal blood pressure was 115 mm Hg systolic and 70 mm diastolic. The highest blood pressure reading was 145 mm Hg systolic and 90 mm diastolic, taken 1 minute after the immersion. There was no constitutional reaction, but the hand was reddened and slightly swollen. The patient said the hand throbbed.

A series of injections of testosterone propionate and later of estrogenic hormone were without apparent effect. A large amount of histaminase was again given without effect.

In October 1939 the patient was sent to the Mayo Clinic for investigation. The hand did not swell when immersed in cold water but the application of ice cubes to the skin still produced wheals. Regardless of "desensitization" with cold water over a

period of a month, the wheals could still be produced. There were no significant findings in the laboratory studies, which included blood cell counts, platelet and reticulocyte counts, blood smears, bleeding time, clot retraction time, vitamin C determination, and urine examination for lead and arsenic. The urinalysis was normal. A biopsy of the skin showed only the lesions of purpura.

The patient was urged to move to Arizona, which he did. Upon the advice of Dr. Bayard T. Horton of the Mayo Clinic he continued taking showers daily, beginning with warm water and allowing the water gradually to become cool. A report received on June 4, 1940, indicated that the patient was very much better. He was wearing short underwear for the first time in five years. The purpuric lesions of the ears had cleared up and he was using ear muffs only at night, the latter since it is quite cool at night in Phoenix. The ankles were still swollen, but the hemorrhagic areas on the ankles and feet had disappeared. The bluish discoloration which had extended up the legs and thighs was entirely gone. He had tested himself by applying a chilled bottle to the skin without a local reaction. He had not resumed working.

However, a report on September 16, 1941 was not so favorable. In a letter the patient stated as follows:

"I haven't made anything like the improvement I had hoped the summer heat out here would produce. However, the summer this year was not as hot as usual, so I am told. The highest official temperature this year has been 108 degrees, whereas the natives here tell me it usually goes to 118 and 120.

"I should have written to you long before this, but when one is sick everything is neglected. The swelling has left my feet and legs, but if I do much walking or sit still for any length of time my feet swell and cause me considerable pain. There is very little improvement in the color of my feet and legs, in fact I believe my right ankle is darker. It is almost black.

"I dread for the winter to come, as the least drop in temperature, or the least cool wind, causes my ears, feet and legs and sometimes my hands to hemorrhage. Was down town in one of the air-cooled stores today and my right ear began to tingle. When I got home I had a small new hemorrhage on it."

COMMENT

This is a case of cold allergy associated with purpura hemorrhagica of the affected, mainly acral, parts. The earlier urticarial reactions gradually subsided, leaving the purpuric manifestations of the ears, hands and feet as the outstanding feature of the case. There were no general or constitutional reactions on exposure to cold. At least two episodes are recorded, however, of hemorrhagic renal lesions which probably were purpuric in nature. No blood dyscrasia could be demonstrated. In spite of the definite cold allergy disclosed, there was no therapeutic response to the usual methods employed and found to be satisfactory in other cases of cold allergy. Apparently beginning as a simple cold allergy the condition finally became one of persistent purpura hemorrhagica of the acral parts with the evidence of cold allergy still persisting in the form of urticaria that could be induced locally by the application of cold objects to the skin. A similar case has not been previously reported.

BIBLIOGRAPHY

1. BOURDEN. Quoted by Horton, Brown and Roth.⁶
2. BLACHEZ. Quoted by Horton, Brown and Roth.⁶

- 3 DUKE, W W Urticaria caused specifically by the action of physical agents, Jr Am Med Assoc, 1924, lxxxiii, 3
- 4 LEWIS, T The blood vessels of the human skin, etc, 1927, Shaw and Sons, Ltd, London
- 5 HORTON, B T, and BROWN, G E Systemic histamin-like reactions in allergy due to cold, report of six cases, Am Jr Med Sci, 1929, clxxii, 191
- 6 HORTON, B T, BROWN, G E, and ROTH, G M Hypersensitiveness to cold, Jr Am Med Assoc, 1936, cvii, 1263
- 7 VAUGHAN, W T Practice of allergy, 1939, C V Mosby Co, St Louis

SYPHILITIC PAN-MENINGITIS (SO-CALLED CHRONIC HYPERTROPHIC SPINAL PACHY-MENINGITIS) *

By GORDON R KAMMAN, M D, F A C P, *Saint Paul, Minnesota*, and
A B BAKER, M D, Ph D, *Minneapolis, Minnesota*

THE case about to be reported belongs to the group of disorders erroneously referred to as "chronic hypertrophic spinal pachymeningitis." We say "erroneously referred to" because in most cases reported, the leptomeninges as well as the dura were adherent and involved in the pathological process. Since the detailed histological studies in our case provide additional evidence that the pathological process is something more than a hypertrophic "pachymeningitis" and since such cases are comparatively rare, a report of the present case seems justified.

Syphilis and tuberculosis have been considered the chief etiological agents in this disease, the former being by far the more common. Occasionally one encounters cases ascribed to trauma or to pyogenic infections. Invasion by pyogenic organisms is more prone to result in a *peripachymeningitis*. Peripachymeningitis was first described by Traube in 1871. In this condition there is combined inflammation of the spinal meninges (dura and arachnoid) and the epidural connective tissue situated between the dura and the periosteum of the vertebrae¹. The main pathologic changes occur in the *perimeningeal* tissues which become infiltrated with pus or transformed into "sclerotic tissue." In syphilitic "pachymeningitis", however, the process is restricted to the dural and intradural regions, the extradural tissues escaping. Both conditions may produce degenerative changes in the white matter of the spinal cord which, in some instances, resemble *tabes dorsalis*.

"Chronic hypertrophic spinal pachymeningitis" is essentially a chronic inflammatory reaction consisting of a fibrous hyperplasia of the dura, with perivascular and interstitial infiltration of lymphocytes and plasma cells. This infiltration is most intense near the inner layers of the dura, and is frequently continuous with the pathological process involving the underlying leptomeninges and spinal cord. The cord itself shows varying degrees of myelomalacia with demyelination of various fiber pathways and degeneration of the ganglion cells. The cord changes are thought to be due either to constriction of the blood vessels

* Received for publication September 17, 1940

From the University of Minnesota Department of Nervous and Mental Diseases, Ancker Hospital Division, Saint Paul, Minnesota, and the Department of Neuropathology

supplying the cord by the thickened meninges or to a compression of the spinal roots with obliteration of the perineural subarachnoid spaces

The symptoms of "chronic hypertrophic spinal pachymeningitis" present no pathognomonic features. They may vary from day to day, and in some cases have been mistaken for symptoms of hysterical origin. The distribution of neurologic signs is determined by the portion of the spinal cord that is involved. Although the disease has a particular affinity for the lower cervical region, it may develop at any level of the spinal cord. In our case the changes were confined exclusively to the lower segments. The disease cannot be regarded as an exclusively localized process, for it is merely a regional manifestation of a more generalized meningovascular syphilis. In many cases the symptoms are similar to those of spinal cord tumor with root pains, muscle atrophy and areflexia at the level of the lesion, and pyramidal signs below. There usually is ataxia and, with lesions in the cervical cord, there may be sensory dissociation. In some cases the symptoms may render difficult the differential diagnosis from syringomyelia. In fact, for many years there existed a controversy as to whether the thickening of the membranes was secondary to a condition of syringomyelia. This controversy can now be considered as settled since it is generally agreed that constriction of the cord vessels by the thickened meninges can produce central cavitation which may extend for a considerable distance from the lesion.

In the diagnosis of hypertrophic meningitis, examination of the cerebrospinal fluid may prove helpful. In many cases the Queckenstedt test is positive. Further, if a radiopaque medium is introduced into the spinal subarachnoid space and studied roentgenographically, the upper margin of the shadow is usually streaked and broken. This picture is distinct from that produced by an intraspinal tumor. Examination of the cerebrospinal fluid reveals an increase in the total protein. The fluid may be xanthochromic, and, in cases due to syphilis, the serologic tests are usually positive. However, as in our case, the fluid may, at first, give negative complement fixation tests.

CASE REPORT

B. L., a single man aged 54 years, entered the Ancker Hospital in Saint Paul on June 9, 1938 complaining of pain in the back, pains in both legs, numbness of the feet, gait difficulty, sleeplessness, difficulty in urination, and constipation. He stated that six weeks previously he had "caught cold" and following this had noticed a sharp continuous pain in the left knee. This pain radiated up and down the lateral side of the leg, and was aggravated during cold damp weather but not by motion. For 10 days there had been pain in the right leg similar to that in the left, and both feet had been numb. During the three or four days preceding hospitalization there had been some difficulty in walking, but the patient was unable to state the exact nature of this interference. Constipation had been severe—"there seemed to be an obstruction in the rectum." There also was difficulty in emptying the bladder, but no involuntary urination. The past history was not contributory except for the fact that the patient had had gonorrhea 30 years before, and about 12 years before admission had suffered a penetrating wound of the left eye resulting in almost complete loss of vision and in the gradual development of an external squint.

The neurological examination revealed an exotropia of 25 on the left with an old, dense, sickle-shaped corneal scar, opacity of the lens, and an irregular iris. The right eye showed a 25 exotropia with ptosis of the lid and a paradoxical pupil. The right knee jerk was normal, but the left knee jerk and both ankle jerks were absent. There

was bilateral ataxia in the knee-heel tests, deep pain and position sense were lost in both feet. Light touch and superficial pain sense were impaired from the eleventh dorsal dermatome downward.

The physical examination was essentially negative except for a moderate degree of peripheral arteriosclerosis and a grade 1 enlargement of the prostate. Blood pressure was 150 mm of Hg systolic and 96 diastolic, and tests for renal function gave normal results.

The cerebrospinal fluid was yellow in color, under 16 mm Hg pressure, and showed no rise upon jugular compression. Globulin was 3 plus, there were 30

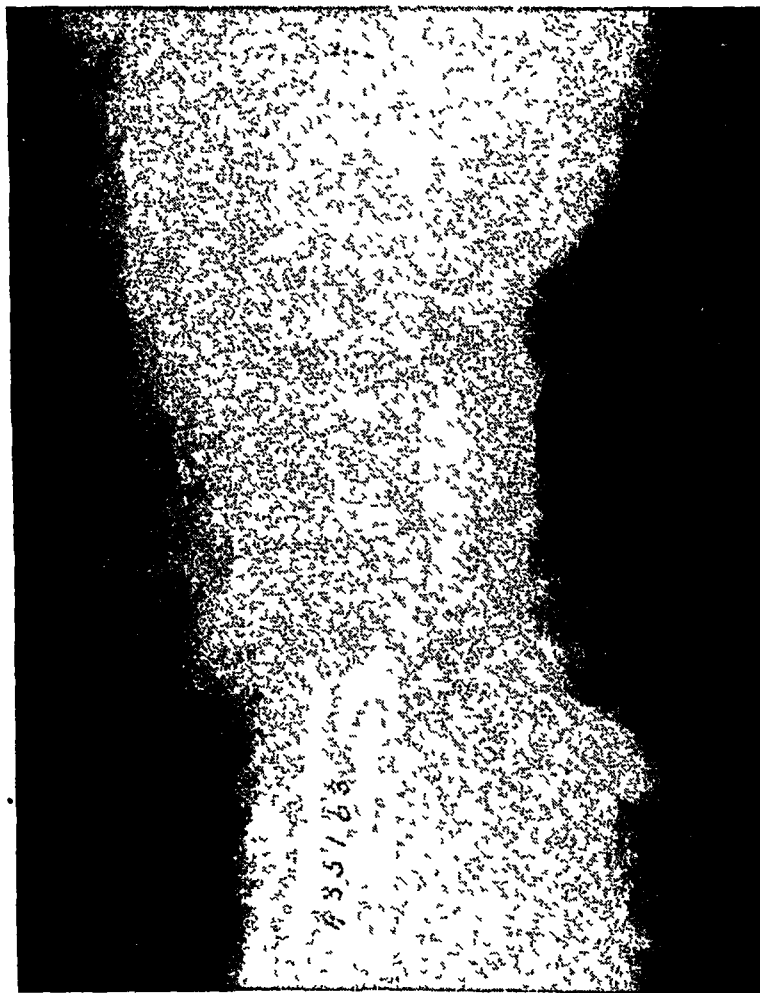


FIG 1 Roentgen-ray showing the complete block of the Lipiodol between the second and third lumbar vertebrae. The irregular conical shape is very suggestive of adhesions.

lymphocytes per cu mm, the Wassermann reaction was negative, and the colloidal gold curve read 0000145300.

After some rather desultory treatment under which the pain and the bladder function improved, the patient was discharged from the hospital on August 4, 1938. He reappeared on September 28, 1938, saying that the pains in his legs were worse and his urinary retention was again troubling him. The examination gave essentially the same findings as on the previous admission. The patient was treated symptomatically. On January 18, 1939 a spinal tap produced deeply yellow fluid, and there was no rise on jugular compression. The cerebrospinal fluid chlorides were 613 mg per 100 c.c., the protein 268 mg per 100 c.c., glucose 204 mg per 100 c.c. Wassermann reaction

4 plus, and the colloidal gold curve 0255543210 Treatment was continued with neoarsphenamine and sodium iodide

On March 5, 1939, examination by another member of the staff showed both pupils to be fixed to light and the right to be larger than the left The right fundus was normal and the left was not visualized because of the corneal scar There was a left exophoria The lower extremities showed pitting edema of both feet, with the right leg fixed in semiflexion, although the knee could be passively flexed to a slight degree There was some movement of the left lower extremity at the hip, but the flexors and the extensors of the left leg were paralyzed There was atrophy of both hamstring groups Touch and pain sensation were impaired on the left side from the inguinal region downward, and on the right side from the knee down There was impaired touch and pain sense over all of the sacral dermatomes bilaterally A note was made to the effect that the eleventh dorsal spinous process seemed to be somewhat more prominent than the others Spinal tap below the second lumbar spine gave



FIG 2 Cross section through the region of the cauda equina The entire spinal canal is filled by this chronic granulation With careful study one can identify the thickened dura at the periphery

clear, slightly yellow fluid under 110 mm water pressure, rising to 180 mm on jugular compression Below the fourth lumbar vertebra the pressure readings were the same as below the second lumbar spine The cerebrospinal fluid contained 182 mg protein per 100 c c, 162 mg glucose per 100 c c, gave a positive Wassermann reaction, and a colloidal gold curve of 1554433100

On March 10, 1939, after considerable discussion by various members of the staff, 50 c c of Lipiodol were injected into the lumbar subarachnoid space Roentgenographic studies showed complete block in the ascent of the oil at the level of the inferior border of the disc between the second and third lumbar vertebrae With the patient in the Trendelenburg position, the superior border of the oil was seen to be sharply irregular and conical, suggesting adhesions rather than protruding disc or tumor type of block (figure 1) The oil moved freely into the inferior sac with no appreciable disturbance in outline in the lumbosacral area The spine showed a slight generalized hypertrophic arthritis, a marked accentuation of the lumbosacral angle, and a spondylolisthesis grade one There was a spina bifida defect in the fifth lumbar and first sacral vertebrae

On March 14, 1939, again after considerable discussion, an exploratory laminectomy was performed. The laminae of the second, third, and fourth lumbar vertebrae were removed, and an attempt was made to open the dura. The subarachnoid space was found to be completely obliterated except in the extreme upper and lower ends of the incision. The lipiodol was removed from the lower end of the incision. The dura was closed with interrupted silk sutures, and the muscles, fascia and skin were closed in layers. The patient rapidly failed and died six hours after the operation.

At *autopsy* the significant findings were confined to the nervous system. There were no evidences of visceral syphilis. The brain showed considerable accumulation



FIG 3 Section through the thickened dura. The meningeal membrane is markedly thickened, fibrosed and partially hyalinized. Its inner surface is attached to the more cellular elements which fill the spinal canal.

of subarachnoid fluid. On cut section there was a small area of softening in the right basal ganglia. The brain was not studied microscopically. The external examination of the cord revealed a diffuse thickening of the pia-arachnoid, most marked in the lower levels. In the lumbar region the leptomeninges were firmly adherent to the dura, while in the region of the conus, these inner cord membranes had become completely obliterated by a firm rubbery mass which extended from the dura to the cord and was most extensive in the right lateral aspects of the cord. Here the spinal nerves were completely incorporated in the pathologic process. On the left lateral surface of the cord there was no such involvement, but the cord itself was moderately displaced and compressed to the left. Inferiorly in the region of the cauda equina this rubbery involvement increased in extent to include all structures in the spinal

canal so that the entire canal was filled by this rubbery substance which grossly had a lamellated appearance due to the presence of the numerous nerves whose outlines could hardly be made out. In this region the entire process was surrounded by a very greatly thickened dura which in some areas measured about 1 mm in thickness and whose inner surface was firmly incorporated in the pathologic process (figure 2). The terminal 4 cm of the cauda appeared free and uninvolved.

Microscopically, sections through the cauda equina in the regions of the most severe involvement revealed a thickened dura which could be clearly distinguished from the surrounding process. The dura had greatly thickened throughout its circum-



FIG 4 Chronic granulation tissue. This tissue comprises the bulk of the inflammatory elements. Even with this moderate magnification one can identify lymphocytes, fibroblasts and giant cells.

ference and had undergone a dense fibrosis and in many areas a hyalinization (figure 3). Scattered throughout this altered dura were many scattered hemorrhages. The outer surface of the dura was invaded by numerous mononuclear cells, most of which remained localized to its superficial layers. The inner dural tissues presented a most extensive cellular alteration. This alteration was directly continuous with the extensive pathologic process which filled the spinal canal in this region (figure 4).

The entire area within the dura was replaced by a granulomatous process which had completely eradicated all structural architecture. It was impossible to identify the leptomeninges or the nerve roots (figure 2). Only in scattered areas could one observe with special stains an occasional naked axis cylinder or an axon surrounded by

the outline of a myelin sheath. The entire region was occupied by a chronic granulomatous process composed primarily of actively proliferating fibroblasts and strands and bundles of collagen. Intermixed with this connective tissue were numerous small lymphocytes, plasma cells, scavenger cells, and even an occasional leukocyte. This inflammatory process appeared to have extended outward from the inner layer of the dura with which it is intimately connected and to have penetrated the spinal canal, replacing the nervous structures (figures 2 and 3).

Necrosis was uncommon, and in the most severely involved regions only a single necrotic area was observed. This area was surrounded by a rim of small lymphocytes.

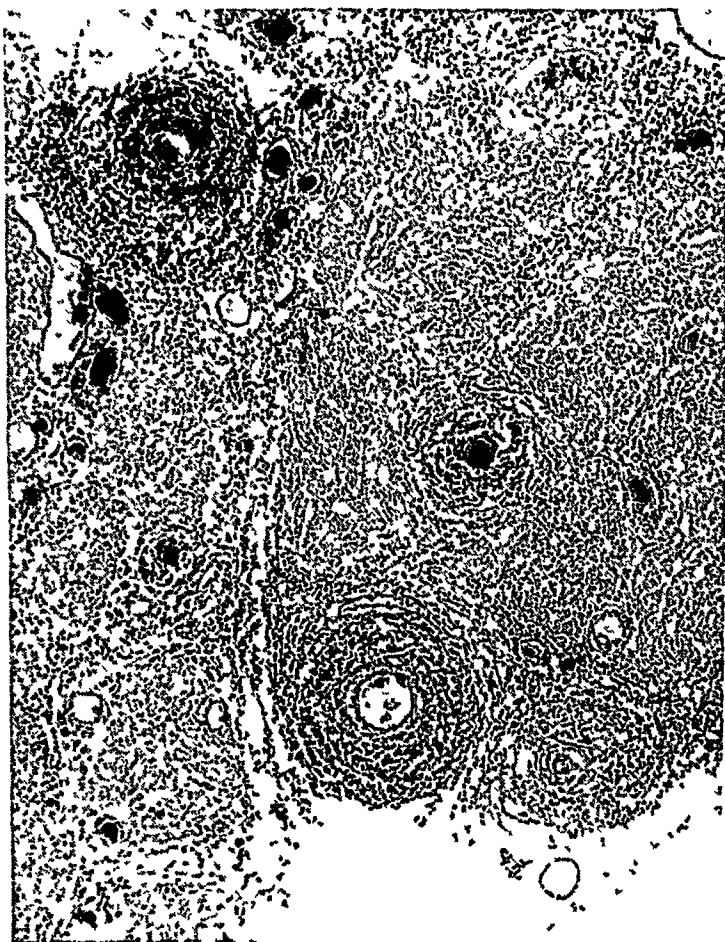


FIG 5 Low magnification showing the extensive vascular involvement. These vessels present a typical Heubner's panarteritis. In one vessel the entire lumen has been occluded by an intimal proliferation.

and fibroblasts among which could be found an occasional giant cell. It had the appearance of a small gumma.

The blood vessels within this involved tissue presented very striking and characteristic findings. The larger vessels, especially those situated near the periphery and probably representing the meningeal vessels, showed mostly a fibrosis of the wall elements with a marked thickening of the vessel. The intima was proliferated and in many cases completely obliterated the vessel lumen. There was little or no cellular invasion into these vessels. The smaller vessels, especially those situated more centrally, presented the typical panarteritis described by Heubner (figure 5). All the wall elements were completely infiltrated by lymphocytes and plasma cells. In many

vessels the cellular reaction was so extensive that no vessel structure could be identified. Some of the vessels were occluded by endothelial proliferation (figures 5 and 6).

In the adjacent regions of the spinal cord the structural changes were very similar but less extensive. In spite of an almost complete demyelination and a partial fragmentation of the axons, both cord and rootlet tissue could be identified in the region of the conus. In some isolated areas definite axons surrounded by moderately intact myelin were observed. However, throughout this region the granulomatous process infiltrated everywhere. In the lumbar cord the pathologic process was much less extensive. The cord architecture was intact, there was an extensive perivascular and

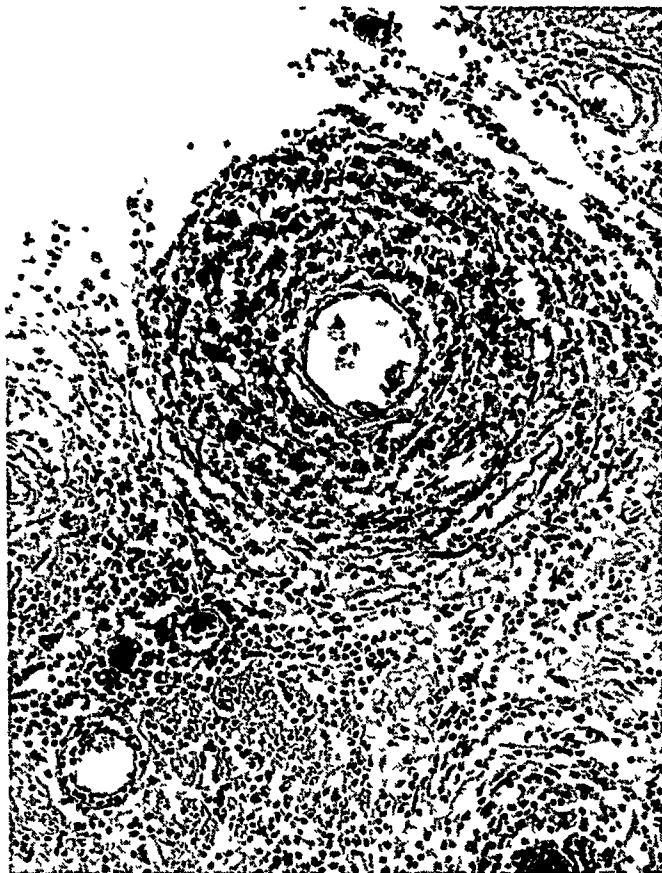


FIG 6 Heubner's panarteritis, high magnification. Note the round cell invasion of all layers of the vessel wall. A beginning secondary fibrosis is becoming apparent. The vessel lumen is still patent.

diffuse lymphocytic infiltration involving both the gray and the white substance especially in the dorsal half of the cord. The meninges and the spaces along the dorsal aspect of the right side of the lumbar cord were obscured by the granulomatous process which in certain localized areas had penetrated through the pia into the posterior columns. Inflammatory tissue here resembled that already described in the region of the filum. The right posterior rootlets were enmeshed within the granulomatous tissue and showed extensive alterations. The rest of the rootlets in this region were intact. The leptomeninges were moderately fibrotic but otherwise normal.

All levels of the cord above the midlumbar region appeared to be intact histologically, except for a very mild thickening of the leptomeninges and a secondary involvement of the long sensory tract.

SUMMARY AND CONCLUSIONS

1 So-called "*chronic hypertrophic spinal pachymeningitis*" is in reality a pan-meningitis

2 Syphilis and tuberculosis have been considered the chief etiological agents, the former being by far the more common

3 The perimeningeal tissues are not involved

4 In syphilitic pan-meningitis there is fibrous hyperplasia of the dura which is continuous with the pathological process involving the underlying leptomeninges and spinal cord. The cord shows varying degrees of myelomalacia with demyelination of various fiber pathways and degeneration of ganglion cells

5 While this disease has a particular affinity for the cervical region, it may develop at any level of the spinal cord

6 A case of syphilitic pan-meningitis involving the lower portion of the spinal cord is reported with autopsy findings

BIBLIOGRAPHY

HASSIN, G. B. Circumscribed suppurative (non-tuberculous) peripachymeningitis. Histopathologic study of a case, *Arch. Neur. and Psychiat.*, 1928, xx, 110-129

SUBACUTE BACTERIAL ENDOCARDITIS CAUSED BY A HITHERTO UNDESCRIBED GRAM NEGATIVE COCCUS *

By GUSTAVE J. DAMMIN, M.D., *San Juan, Puerto Rico*

INTRODUCTION

THE following report concerns a case of calcific aortic stenosis with superimposed subacute bacterial endocarditis caused by a hitherto undescribed gram negative coccus. The literature on the occurrence and specific features of subacute bacterial endocarditis in the older age groups has recently been reviewed by Bayles and Lewis¹. From a study of 28 patients over 40 years of age, they concluded that subacute bacterial endocarditis in this age group was (1) less frequently correctly diagnosed, that (2) heart failure and azotemia occurred more frequently, and that (3) bacteremia was more difficult to demonstrate.

The bacteriology of endocarditis was the subject of a recent study by Shilling². Among the organisms cited as causative agents, there was one designated as a gram negative micrococcus, which was isolated from a case described by Coulter³. Shilling isolated from one of his cases of subacute bacterial endocarditis a gram negative coccus which could not be classified. The organism recovered from the case to be presented did not resemble the gram negative cocci isolated from previously reported cases. Since the organism had not been described previously, it was considered worthy of study.

* Received for publication August 20, 1940

From the Medical Clinic and Pathological Department of the Peter Bent Brigham Hospital, Boston

CASE REPORT

The patient, P F, was a 66-year-old white male who entered the Peter Bent Brigham Hospital on October 30, 1939, because of weakness and insomnia of one month's duration. There was no family history of rheumatic fever, scarlet fever or heart disease. The patient had always used tobacco, but never alcohol, to excess. As a child he had had scarlet fever and pertussis, and had been subject to frequent epistaxes. There was no past history of tonsillitis, chorea or upper respiratory infections. In 1896, at the age of 24, the patient had fever and migratory joint pains for which he was confined to bed for six months. He was told that he had rheumatic fever but that his heart was not affected. He had never had hemoptyses, precordial pain or attacks of syncope. There was no evidence that the patient had ever had gonorrhea or syphilis.

The present illness began about one month before admission when the patient contracted a cold which was accompanied by cough, sputum and nasal discharge. He complained of anorexia, insomnia, malaise and pains in the legs. During the week preceding admission, ankle edema and dyspnea on exertion appeared. There had been no recent noticeable weight loss.

Physical examination revealed a well developed, elderly, moderately dyspneic, undernourished man with normal temperature and pulse rate. Over the chest and extremities there were scattered telangiectases. There were no petechiae in the skin or mucous membranes. There were bilateral lenticular opacities which interfered with light perception and examination of the fundi. The throat was injected and the few remaining teeth showed extensive caries with associated pyorrhea alveolaris. The heart percussion outline showed enlargement to the left and downward. The rhythm was regular. There were no thrills. A high pitched early diastolic murmur was audible from the aortic area to the third left interspace. In the aortic area there was a rough systolic murmur of moderate intensity which was transmitted to the carotids. At the apex there was a long, loud systolic murmur. The pulmonic second sound was accentuated. The pulses were collapsing in type, but no capillary pulse was demonstrable. The blood pressure was 110 mm of Hg systolic and 44 diastolic. Râles and dullness were present at both bases. Neither the liver nor the spleen was palpable. Crepitation was demonstrable in both knees. The finger tips were not tender nor was there clubbing of the fingers or toes. There was slight pitting over the tibiae.

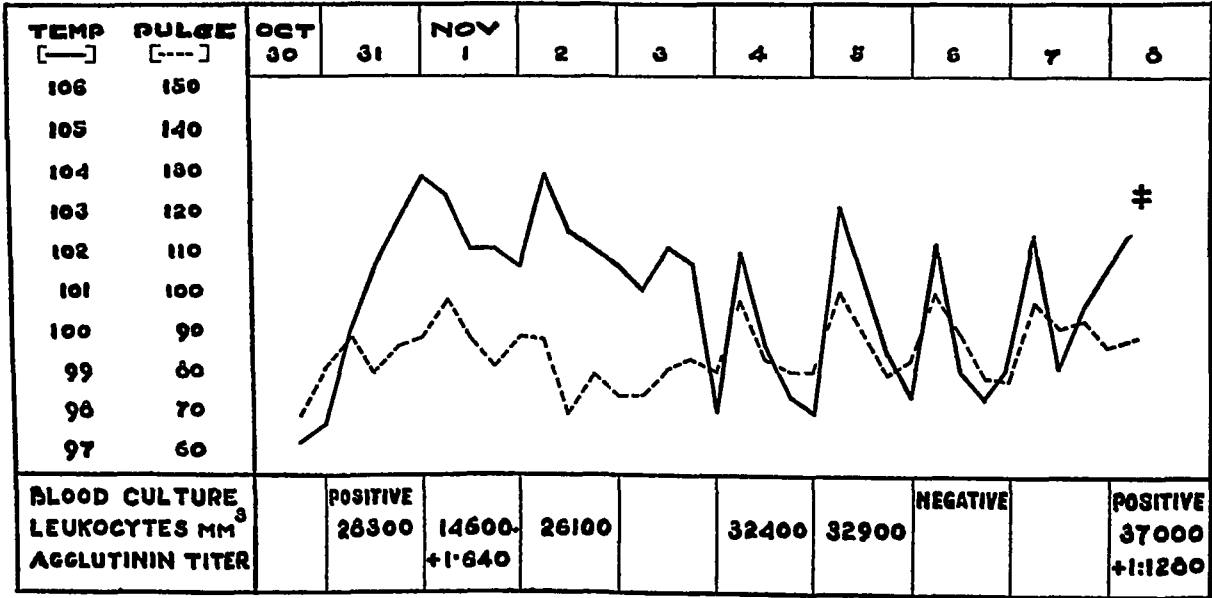
The erythrocyte count was 2.73 million and the leukocyte count was 26,000 per cubic millimeter. The hemoglobin content was 60 per cent (Sahli). The differential leukocyte count showed 91 per cent neutrophils, 5 per cent lymphocytes and 4 per cent monocytes. The mean corpuscular volume was 114 cubic microns, the mean corpuscular hemoglobin, 30 micromicrograms, the mean corpuscular hemoglobin concentration was 26 per cent, and the volume of packed erythrocytes, 31 per cent. The icterus index was 15. Blood Wassermann, Hinton and gonococcus complement fixation tests were negative. The urine was normal.

Admission diagnosis was rheumatic heart disease with aortic stenosis and insufficiency and subacute bacterial endocarditis.

The course was one of gradual downward progression. The fever initially was of a high grade remittent type which after five days became intermittent (see chart). The patient was cooperative on admission but soon became irrational and restless. Shaking chills accompanied the rises in temperature. A chest film showed the transverse cardiac dimension to comprise 65 per cent of the internal transverse diameter of the thorax, indicating cardiac enlargement. Fluoroscopy revealed an irregular mass of calcification in the region of the aortic valve. The electrocardiogram demonstrated left axis deviation. Albuminuria and microscopic hematuria were

present on several occasions The plasma non-protein nitrogen rose from 19 to 41 milligrams per cent The leukocytosis remained throughout the course (see chart) The capillary fragility as tested with the sphygmomanometer was normal Sputum culture showed *B. proteus* and non-hemolytic *Staphylococcus aureus* Two of the three blood cultures were positive Digitalis, instituted on November 2, did not alter the downward trend of the patient's course Because of rigidity of the neck which appeared on November 8, lumbar puncture was performed with, however, normal findings Sulfanilamide was begun late in the course and did not influence the progressive decline The spleen did not become palpable but petechiae appeared in the palpebral conjunctivae On November 9, after sudden onset of respiratory difficulty, the patient died

Autopsy was performed two hours post mortem The skin and mucous membranes were pale and petechiae were noted in the conjunctivae and over the buttocks There was moderate pitting edema over the sacrum



CASE P.F. - SUBACUTE BACTERIAL ENDOCARDITIS

FIG 1 Subacute bacterial endocarditis caused by a hitherto undescribed gram negative coccus

The heart weighed 440 grams There was left ventricular hypertrophy and the auricles were dilated The tricuspid and pulmonic valves were normal The mitral valve was thickened and opaque The free edges were nodular but there was no calcification The mitral orifice was not stenosed The chordae tendineae and papillary muscles were normal

The aortic valve presented on its left anterior cusp, a large, red, warty and friable vegetation measuring 3.0 by 1.5 centimeters A smear of the cut surface showed numerous small gram negative cocci On the right anterior cusp there was another warty friable vegetation measuring 1 cm in diameter Just proximal to this vegetation there was a small calcified plaque There was a large calcified plaque in the aortic ring above the posterior cusp and another calcified area in the margin of the posterior cusp The commissures between the aortic cusps were obliterated and the free margins were adherent 0.5 to 1.0 cm radially from the aortic ring The body of the aortic vegetation consisted of hyaline staining material with several dark staining areas (calcium) proximally and large lighter staining areas, consisting of masses of

bacteria, distally. The surface of the vegetation was covered by a layer of fibrin in which many erythrocytes and polymorphonuclear leukocytes were enmeshed (see photomicrograph).

Grossly, the myocardium showed no fibrosis or softening. Microscopically, there were many scattered clusters of polymorphonuclear leukocytes. There were also small areas of fibrosis showing infiltration with polymorphonuclear leukocytes.



Aortic Vegetation

FIG 2 (A) Masses of gram negative cocci and erythrocytes covering vegetation (B) Fibrin layer with enmeshed leukocytes (C) Calcific deposit in aortic valve

The orifices and lumina of the coronary arteries were of normal patency throughout. In the aortic arch, 3 cm above the aortic ring, there was an ulcerated calcified atheromatous plaque measuring 1 cm in diameter.

The pericardial cavity contained 50 c.c. of cloudy yellow fluid which on smear showed many polymorphonuclear cells and minute gram negative cocci. The pericardial surfaces were injected. Microscopic section of the pericardium showed nu-

merous collections of polymorphonuclear cells and scattered hemorrhages. The epicardium also showed infiltration with polymorphonuclear leukocytes.

The right pleural cavity contained 250 cc and the left, 500 cc of yellowish, slightly turbid fluid. The right lung weighed 625, and the left, 540 grams. Extensive emphysema was present. The cut surfaces of the lungs were moist and congested, and showed scattered dark red mottled areas. Microscopically, the alveoli adjacent to the bronchioles were seen to be distended with polymorphonuclear and mononuclear leukocytes.

The spleen was firm and weighed 290 grams. There were no adhesions and the pulp was not soft. The liver weighed 1590 grams, was of normal consistency and showed no adhesions. The cut surface presented a nutmeg appearance. Microscopic sections showed the tributaries to the central veins distended with erythrocytes and the liver cells adjacent to the center of the lobule to be vacuolated and poorly staining.

The right kidney weighed 180, and the left, 200 grams. In the left kidney there was a yellow wedge-shaped infarct measuring 1 cm in diameter. Subcapsular petechiae were present in both kidneys. Microscopically, the glomerular tufts were congested and the tubules distended with amorphous debris and erythrocytes.

The brain weighed 1200 grams. The vessels were normal but for a single atheromatous plaque measuring 1.5 mm in diameter situated in the right anterior cerebral artery. There were no hemorrhages or aneurysms.

Anatomic diagnosis: Subacute bacterial endocarditis, rheumatic heart disease, inactive, with aortic stenosis and incompetency, calcification of the aortic valve, arteriosclerosis of the aorta, hydrothorax, bilateral, due to passive congestion, infarction of kidney, left, healed, due to embolism.

BACTERIOLOGY AND IMMUNOLOGY

From the blood cultures taken on October 31 and November 8, the gram negative coccus to be described was isolated. The blood culture of November 6 was negative. The gram negative coccus was not recovered from the post-mortem blood culture. One of the aortic vegetations was immersed in phenol, sectioned with sterile precautions, and the cut surfaces streaked on blood agar plates. In these cultures, the gram negative coccus was present but in a rougher phase than that recovered from the antemortem blood cultures. *B. proteus* was recovered from the sputum, stool and postmortem blood culture. Studies on the gram negative coccus and the *B. proteus* will be discussed separately.

Gram Negative Coccus: When this organism was isolated from the antemortem blood cultures (to be designated "AM"), it had the characteristics of an R (rough) phase organism. The growth on a blood agar plate after 48 hours' incubation at 37° C in a moisture jar, consisted of minute, dark gray, dry, granular colonies measuring less than 1 mm in diameter. Under the microscope the surface of the colony appeared dull and the edge was irregular. The colonies were firm in consistency and were removed from the medium with difficulty. The colonies produced neither green pigment nor hemolysis on blood agar. The organisms from these colonies did not enter into suspension in saline but precipitated spontaneously. Growth in dextrose serum broth was granular and produced minimal diffuse clouding. The organism cultured from the vegetation (to be designated "V") appeared to be in a still rougher phase and produced no clouding in dextrose serum broth.

For several months subsequent to initial isolation, these organisms were fastidious in their growth requirements. Serum or blood, as well as moisture, was

required For the six months' period of observation, cultures of the "AM" and "V" organisms were transferred to freshly prepared blood agar plates or slants every 72 to 96 hours

After three weeks of continued subculturing, the blood agar plate cultures of the "AM" organism showed occasional grayish white colonies which measured 1.5 to 2.0 mm in diameter Under the microscope the surface was even and the edge entire without projections The colonies were moist in appearance and soft and butyraceous in consistency In dextrose serum broth, these organisms produced a diffuse clouding and in saline remained in suspension On blood agar, the colonies were surrounded by an area of greenish pigmentation, but no beta hemolysis After three months, the blood plate cultures of the "V" organism showed colonies resembling the S (smooth) phase described for the "AM" organism above

Morphology and Staining Characteristics The "AM" and "V" organisms were morphologically identical Throughout the six months' period of study, there was no change in the morphology of these organisms Varying degrees of pleomorphism were always present, however The predominant form always was a gram negative coccus measuring 0.5 to 0.7 micron in diameter There were occasional diplococcus and coccobacillary forms The long axes of the paired cocci were not parallel, as with the meningococcus, but were in the same axis These forms were more numerous when the organisms were cultured in liquid media Old cultures showed swollen coccal forms measuring 1.0 to 2.0 microns in diameter The organisms were constantly gram negative, at no time were gram positive forms present They stained readily with methylene blue and showed no metachromatic staining Using the Ziehl-Neelsen technic, they were not acid fast The organisms were non-spore forming, non-motile and non-encapsulated

Physical Growth Requirements Optimum growth occurred at 37° C in a moisture jar Growth was equally good at 37° C at 10 per cent carbon dioxide tension Twenty-four hour dextrose broth cultures of the S phase of both the "AM" and "V" organisms did not withstand exposure to 56° C for 15 minutes There was no growth at 22° C under either aerobic conditions or in a moisture jar No growth occurred under strict anaerobic conditions, but there was moderate growth in a hydrogen-carbon dioxide-palladinized asbestos system

Cultural Requirements and Reactions As stated above, for several weeks to months after initial isolation, both organisms required either a serum or blood containing medium Later, however, growth was accomplished in plain beef infusion broth and on plain agar, but growth was always scanty Broth cultures invariably showed a tenacious pellicle adherent to the bottom of the tube Good growth occurred in 0.15 per cent agar after 48 hours, but growth was slow on serum glucose agar and egg slants* Very scant growth occurred on desoxycholate agar (Leifson) There was no growth on Simmons citrate agar, indicating an inability to utilize citrate Moderate growth appeared on chocolate agar The growth on Kligler's iron agar (Difco) indicated a production of acid but not hydrogen sulphide

Twelve hour cultures of the "AM" and "V" organisms produced moder-

* These studies were performed at the National Institute of Health through the courtesy of Dr Sara E Branham

ately active reduction of methylene blue Catalase was demonstrable in all cultures from the time of initial isolation to the end of the period of study Oxidase was tested for at monthly intervals with a 1 per cent solution of dimethyl-para-phenylene-diamine hydrochloride,⁴ but was never demonstrable Indol was not produced by either organism when tested for on five day peptone water cultures Five-day 0.1 per cent potassium nitrate broth cultures of both organisms showed the presence of nitrite (Gries-Ilosva method)

Fermentation Reactions Acid was produced on dextrose, levulose, maltose and mannose peptone water media No gas was produced Lactose, mannite, xylose and sucrose were not fermented All fermentation reactions were observed over a period of 14 days

Immunologic Studies Both organisms were agglutinated in the same dilution by the patient's serum The serum of November 1 was positive in a dilution of 1:640, that of November 8, in a dilution of 1:1280 Both 24 live broth cultures and saline suspensions of the "AM" and "V" organisms in their S phase were used in these agglutination studies Incubation for 3 hours in a 37° C. water bath and overnight refrigeration were used The same antigens were not agglutinated by normal control sera

The patient's sera did not agglutinate *B. tularensis* or *Brucella melitensis* in any dilution The antigens of the "AM" and "V" organisms, used as described above, were not agglutinated by antisera for *B. tularensis*, *Brucella abortus*, *E. typhosa*, Paratyphoid "A" and "B" and *Proteus* OX19*

An antiserum was produced in a rabbit using the S phase of the "AM" organism Live culture was administered intravenously on five occasions over a period of 10 days At the end of this time the rabbit serum agglutinated both the "AM" and "V" organisms in a serum dilution of 1:2560

The rabbit antiserum was used in an attempt to revert the S phase of the "V" organism to the R phase with the features it presented when first recovered from the aortic valve vegetation Twelve hour broth cultures were transferred to whole rabbit antiserum and the rabbit antiserum diluted 1:1 with plain broth Whole control rabbit serum, diluted control rabbit serum and plain broth tubes were also inoculated These cultures were subcultured on blood agar plates each day for five days However, growth on many of the subcultures was poor, and where growth was good, there was no evidence of reversion to the R phase Saline suspensions of the "AM" organism, as well as live broth cultures were set up with therapeutic antimeningococcus serum** This serum agglutinated both antigens in dilutions up to 1:128

An antiserum was available, which had been prepared against a gram negative organism which had proved pathogenic for rabbits and which had been designated *Hemophilus cumcuh* Neither the "AM" nor "V" organisms were agglutinated by this antiserum

Animal Pathogenicity A study of animal pathogenicity was made with both the "AM" and the "V" organisms in the R phase and were repeated when the S phase appeared Large amounts of viable culture in both phases proved to be innocuous for white mice, guinea pigs and rabbits Mice were inoculated intraperitoneally with 0.3 c.c. of a heavy broth suspension of 24-hour blood agar

** Supplied by the Antitoxin and Vaccine Laboratory of the Commonwealth of Massachusetts

slant cultures Guinea pigs received 0.6 c.c. of a similar antigen intraperitoneally and subcutaneously Rabbits were inoculated intravenously with 2.0 c.c. of a similar broth suspension The rabbits and guinea pigs had temperature elevations the day following inoculation, but survived for four weeks After this period, they were autopsied No lesions, including valvular lesions, were demonstrable The mice also survived for four weeks and at autopsy presented nothing relevant Neither the R nor the S phase proved to be pathogenic for the animals tested In an effort to induce pathogenicity, mice were given large amounts of mucin-culture preparations, using both the "AM" and "V" organisms Equal parts of 3 per cent mucin and a heavy broth suspension of 24-hour blood agar slant cultures were used All the mice survived (two groups of four mice each) and after three weeks one mouse of each group was autopsied, again, however, with no lesions demonstrable

B. proteus By cultural and serological reactions, it was found that the same *B. proteus* had been recovered from the sputum, stool and postmortem blood culture Saline suspensions of 24-hour plain agar slant cultures were used for agglutination studies The patient's serum did not agglutinate the *B. proteus* obtained from any of the three sources These antigens were not agglutinated by a high titer antiserum prepared against *Proteus* OX19 The patient's serum of November 1 and 8 showed a positive Weil-Felix reaction in a dilution of 1:80, using *Proteus* OX19 All agglutinations were incubated for three hours in a 37° C water bath and read after overnight refrigeration

The organisms from the three sources showed marked motility in 6-hour plain broth cultures, produced rapid stratiform liquefaction of gelatin and spread rapidly on plain and blood agar Dextrose and xylose were fermented with formation of acid and gas Acid was produced in sucrose after nine days There was no action on lactose, maltose, mannite or salicin Peptone water medium was used with incubation at 37° C and observation for 14 days Five-day peptone water cultures showed no production of indole These reactions satisfy the criteria, as stated by Bergey,⁵ for *Proteus morganii*

DISCUSSION

The main points of interest in this study were (1) the causative organism, (2) its transformation from an R to an S phase, and (3) the presence of a positive Weil-Felix reaction

Since the positive Weil-Felix reaction is of but passing interest in this case, it will be discussed briefly Only 2.8 per cent of routine sera will agglutinate *Proteus* OX19 in a dilution of 1:80⁶ We observed that 40 per cent of patients with *Proteus* urinary tract infections showed positive Weil-Felix reactions and agglutinated their own *B. proteus* In more than half of these instances, the Weil-Felix agglutinins could be absorbed out with the patient's own *B. proteus* In this case, however, a positive Weil-Felix was present, but the patient did not agglutinate his own *B. proteus*, nor was it agglutinated by a high titer *Proteus* OX19 antiserum

Of special interest in this case is the causative organism, an unclassified gram negative coccus, which was recovered from antemortem blood cultures and from the aortic valve vegetation in an R phase and which on continued cultivation

acquired the features of an S phase organism. Such transformation on continued cultivation was noted by Wilson⁸ to occur among members of the genus *Neisseria*. The gram negative coccus described above possesses many of the features ascribed to the genus *Neisseria* and particularly to the *Neisseria meningitidis* or meningococcus. This is suggested by many of its growth characteristics and its agglutination by antimeningococcus serum. The genus *Neisseria* is not composed, however, of serologically distinct groups and cross reactions among the numerous species occur. The lack of pathogenicity for white mice, especially with the use of mucin-culture preparations, the negative oxidase reaction⁴ and the morphology of the organism do not permit the identification of this gram negative coccus with the *Neisseria meningitidis*.

That the organisms recovered from cases of subacute bacterial endocarditis are often in the R phase was reported by Tunncliffe and Woolsey⁹. In a study of 26 cultures of *Streptococcus viridans* observed immediately after isolation from patients with subacute bacterial endocarditis, they found evidences of the R phase in 22 of the cultures. These observers suggested that the R element might be an essential factor in the production of endocarditis. As evidence for this, the studies of Rosenow¹⁰ on the production of endocarditis in rabbits using streptococci possessing features of the R phase, were cited.

SUMMARY

A case is presented of subacute bacterial endocarditis superimposed on rheumatic heart disease with calcific aortic stenosis in an elderly male.

The causative organism, a gram negative coccus which we have been unable to classify, was recovered from antemortem blood cultures and was demonstrable in the aortic valve vegetations by smear, and by cultural and histological methods. The causative organism was agglutinated in high dilutions of the patient's serum.

The gram negative coccus, when first isolated, presented the features of an R phase organism, and during the course of continued cultivation, acquired those of an S phase organism.

The morphological, cultural and serological characteristics of this gram negative coccus suggest, but do not permit an unreserved identification with the genus *Neisseria*.

Note. The author is grateful to Dr. Charles A. Janeway for his kind assistance in the preparation of the material and the manuscript.

BIBLIOGRAPHY

- 1 BAYLES, T. B., and LEWIS, W. L., JR. Subacute bacterial endocarditis in older people, *ANN INT MED*, 1940, XIII, 2154.
- 2 SHILING, M. S. Bacteriology of endocarditis with report of two unusual cases, *ANN INT MED*, 1939, XIII, 476.
- 3 COULTER, C. B. Gram negative coccus causing fatal endocarditis, *Proc. New York Path Soc.*, 1915, xv, 7.
- 4 GORDON, J., and McLEOD, J. W. The practical application of the direct oxidase reaction in bacteriology, *Jr. Path and Bact.*, 1928, xxxi, 185.
- 5 BERGEY, D. H. Manual of determinative bacteriology, 1939, Williams and Wilkins, Baltimore.

- 6 SAVOOR, S R, CASTANEDA, M R, and ZINSSER, H Notes on the Weil-Felix reaction in individuals not suffering from typhus, *Proc Soc Exper Biol and Med*, 1935, xxxiii, 365
- 7 BILLINGS, F T, and DAMMIN, G J To be published
- 8 WILSON, S P Investigation of certain gram negative cocci met with in nasopharynx with special reference to their classification, *Jr Path and Bact*, 1928, xxxi, 477
- 9 TUNNICLIFF, R, and WOOLSEY, C I The presence of "roughness" in streptococcus cultures from endocarditis, *Jr Infect Dis*, 1935, lvi, 116
- 10 ROSENOW, E C Experimental infectious endocarditis, *Jr Infect Dis*, 1912, xi, 210

EDITORIAL

THE ASSOCIATION OF ACUTE PANCREATITIS WITH DIABETES MELLITUS

THE association of the pancreas and, more specifically, of the islet tissue with the diabetic state was realized as the result of animal experiments carried out some 30 years before the discovery of insulin. The further interrelationships between the pancreas and the disease diabetes mellitus in man we are still in the process of uncovering. Among these are the various associations between acute pancreatitis and diabetes mellitus.

It has frequently been observed that during acute pancreatitis a temporary glycosuria may appear. Egdahl¹ reported an incidence of 5 per cent in 105 cases of acute pancreatitis. Guleke,² cited by Walzel, found glycosuria in about 10 per cent of his cases. Shumacker,³ in a review of the literature, found 78 instances of glycosuria in 700 reported cases of acute pancreatitis, an incidence of 11 per cent. He also found that 28 of 55 cases had blood sugar levels above 200 mg per cent.

It is commonly assumed that hyperglycemia and glycosuria during acute pancreatitis are due to destruction or dysfunction of islet tissue resulting from the diffuse necrosis, edema and hemorrhage in the pancreas. Gray and his coworkers,⁴ however, have expressed the belief that the rise in blood sugar levels may result from hepatic dysfunction, and Brocq and Varangot⁵ have advanced the theory that the large amounts of trypsin liberated in acute pancreatitis might have some inhibitory action on insulin.

As opposed to the relative frequency of these reports of disturbed carbohydrate metabolism during the acute stage of pancreatitis, there is a scarcity of published instances of permanent diabetes mellitus following upon recovery from acute pancreatitis. Bernhard,⁶ however, in studying 50 cases of operative recovery from acute pancreatitis, found that diabetes mellitus had

¹ EGDAHL, A. A review of one hundred and five reported cases of acute pancreatitis with special reference to etiology—with report of two cases, *Bull. Johns Hopkins Hosp.*, 1907, xviii, 130–136.

² GULFKE, N., cited by WALZEL, PETER. Zur Diagnose und Therapie der akuten Pankreasnekrose, *Beitr. z. klin. Chir.*, 1929, cxlvii, 3–13.

³ SHUMACKER, H. B., JR. Acute pancreatitis and diabetes, *Ann. Surg.*, 1940, cxii, 177–200.

⁴ GRAY, S. H., PROBST, J. G., and HEIFETZ, C. J. Transient acute pancreatitis, *Ann. Surg.*, 1938, cviii, 1029–1051.

⁵ BROCCQ, P., and VARANGOT, J. Les modifications de la glycémie dans la nécrose aiguë du pancréas, *Jr. de chir.*, 1937, xlix, 177–220.

⁶ BERNHARD, F. Das Auftreten des Diabetes mellitus nach akuten Pankreaserkrankungen (Untersucht an 50 operativ geheilten Fällen), *Klin. Wchnschr.*, 1931, x, 632–637.

appeared in five instances. It is of interest that in a number of cases of this type an interval of months or years intervened between the attack of pancreatitis and the appearance of diabetes. This creates a natural doubt as to whether the pancreatic injury was the cause of the later diabetes. It seems probable, however, that in such instances the acute pancreatitis is followed by a progressive fibrosis and reduction of islet tissue.

Aside from the effect of acute pancreatitis in producing temporary or permanent derangements of carbohydrate metabolism, there is another association between diabetes and pancreatitis which has great interest. From available pathological studies it appears that the diabetic is more subject to attacks of acute pancreatitis than the non-diabetic patient. Warren,⁷ in a study of the pancreas in 484 cases of diabetes mellitus, found acute pancreatitis in four cases, pancreatic apoplexy in two cases, and subacute pancreatitis in six cases. This high incidence (2.4 per cent) is approximately eight times the incidence of pancreatitis found by Hamperl⁸ in a series of 20,000 autopsies. The explanation for the susceptibility of the diabetic to acute pancreatitis is not clear. Rich and Duff,⁹ in this connection, referred to the statement of Babkin¹⁰ that in rabbits hyperglycemia results in the production of an extremely ferment-rich pancreatic juice. Such a juice might, in the presence of minor pancreatic injury or duct obstruction, predispose to autolytic changes in the gland. The presence of ferment-rich pancreatic juice in human diabetics has not, however, been demonstrated.

The occurrence of acute pancreatitis in the diabetic has a very definite clinical importance, since the patient is precipitated into severe acidosis or coma. This combination of diabetic coma and acute pancreatitis is not rare. Root,¹¹ in autopsies on 26 patients dying in diabetic coma, found four instances of acute pancreatitis. Warren,⁷ in 121 cases of coma death, found at autopsy 11 instances of acute or subacute pancreatitis. Bowers and Atkins,¹² in 17 autopsies on cases of diabetic coma, found three examples of acute interstitial pancreatitis. Joslin¹³ states that acute pancreatitis should be considered in any case of diabetic acidosis that does not react favorably to intensive insulin therapy.

⁷ WARREN, SHIELDS. The pathology of diabetes mellitus, 1938, Lea and Febiger, Philadelphia.

⁸ HAMPERL, H., quoted by BOSE, H. Die Pankreatitis. Übersichtsreferat, Zentralbl. f. Chir., 1936, lxiii, 261-263.

⁹ RICH, A., and DUFF, G. Experimental and pathological studies on the pathogenesis of acute hemorrhagic pancreatitis, Bull. Johns Hopkins Hosp., 1936, lviii, 212.

¹⁰ BABKIN, B. P. Blood sugar concentration and the external secretion of the pancreatic gland, Jr. Am. Med. Assoc., 1935, cv, 1659-1662.

¹¹ ROOT, H. F. Diabetic coma and acute pancreatitis with fatty livers, Jr. Am. Med. Assoc., 1937, cviii, 777-780.

¹² BOWERS, JOHN Z., and ATKINS, JOHN L. Acute pancreatitis with diabetic acidosis occurring in the course of diabetes mellitus. (Unpublished.)

¹³ JOSLIN, E. P. Treatment of diabetes mellitus, 1937, Lea and Febiger, Philadelphia, p. 559.

It is obvious that the diagnosis of pancreatitis in the presence of diabetic coma presents serious difficulties. The use of the amylase test in blood and urine may afford data which will usefully supplement the clinical symptoms and signs. In certain instances, however, the findings by the blood amylase test may be deceiving. Further clinical and pathological studies are needed in this field.

REVIEWS

The Pharmacological Basis of Therapeutics By LOUIS GOODMAN, M A, M D, and ALFRED GILMAN, PH D 1383 pages, 26 × 18.5 cm The Macmillan Company, New York City 1941 Price, \$12.50

In writing this comprehensive treatise on pharmacology the authors have had three objectives in mind first, the correlation of pharmacology with the related medical sciences, second, the reinterpretation of the action and uses of drugs from the point of view of the important advances in medicine, and third, the placing of emphasis on the application of pharmacodynamics to therapeutics. The book has been divided into 16 sections, based largely upon the physiological systems of the body upon which drugs act. In addition there is an appendix in which the principles of prescription writing are discussed.

The authors, in preparing this subject matter for the various sections of this book, have made an exhaustive survey of the literature and have not only presented cogent data from various scientific journals but have critically evaluated the experimental work recorded. Historical sketches of the first use of various drugs are found throughout the book particularly in the field of anesthesia and in the development of autonomic drugs. In this the authors have shown a felicity of style uncommon to books of this character.

The physiological approach to many of the subjects is to be commended, particularly the authors' treatment of the pharmacology of the autonomic nervous system where the latest theories of the action of drugs on organs of autonomic innervation are discussed and elucidated from a pharmacologic standpoint.

The book is extraordinarily recent in its references which are given in great detail, and the latest subject matter in the field of pharmacology dealing with the adrenal-cortical hormone, sulfonamide derivatives and vitamins appears to be brought up to the very time of the publication of the book.

The reviewer highly commends this book to the practicing physician and to students in pharmacology or medicine as a standard reference and text for the application of the use of drugs in the treatment of disease.

J C K, JR

Bacillary and Rickettsial Infections By WILLIAM H HOLMES, M D 676 pages, 24 × 16 cm The Macmillan Company, New York City 1940 Price, \$6.00

This is a pleasant, well bound book inescapably reminiscent of Zinsser. Used as a textbook by the author, it combines points of view and is written in a style more literary than that of the usual textbook. The clinical implications are succinctly indicated, and logical therapies are mentioned briefly. Quotations of sources are used, and each seems chosen for its literary style, as well as for medical priority. The Bible and the ancient Greeks are heavily leaned upon, and historical background is journalistically stressed. Except for having specific and accurate data instead of generalities, it might well be a popular volume. Such gallant treatment builds two aspects of bacteriology into a full-sized book. With the world in camps again, however, and the danger of plague so near to us all, it is perhaps not out of proportion. This is a book that can be recommended to students with time to read it, and to lay persons interested in the background of epidemics and in a wellbred perspective on modern medicine.

C A

Cardiac Clinics By FREDERICK A WILLIUS, B S, M D, M S in Med 276 pages, 24.5 × 17 cm C V Mosby Co, St Louis, Missouri 1941 Price, \$4.00

This book is an accumulation of the "Cardiac Clinics" which have appeared previously in the Proceedings of the Staff Meetings of the Mayo Clinic

All of the common and a few of the rare diseases of the heart are considered briefly. Each type of cardiac disease is illustrated with several cases from the files of the Mayo Clinic. A synopsis of the history, physical examination, and laboratory findings of each case is given. This is followed by a concise, formal discussion in which the pertinent diagnostic features are recapitulated and their practical significance stressed. Whenever possible the author has amplified the case studies by noting the important pathological findings. The case studies are usually supplemented with an informal set of questions and answers concerning the particular case or the general type of heart disease under discussion.

The author advises caution in making a diagnosis on the basis of a few isolated findings. He stresses the point that a case may be quite atypical, and that supposedly pathognomonic criteria may either be absent or refer to more than one entity. However, many practical and valuable diagnostic and prognostic maxims are mentioned.

There is a commendable effort made to explain briefly the mechanism by which the pathological physiology occurring in cardiac disease produces abnormal symptoms and physical signs. The chapters on "Functional States" and "Treatment and Management" are exceptionally good.

There are a few statements which justify mild adverse criticism. On page 37, in a discussion of a metastatic adenocarcinoma of the pericardium, the primary site is stated as being in a bronchial node. This is not in keeping with accepted pathological teachings. On page 77 the term *malignant endocarditis* is stated as being synonymous with *subacute bacterial endocarditis*. Although this is permissible, and although the ultimate malignancy of *subacute bacterial endocarditis* is unquestioned, yet the consensus of opinion associates *malignant endocarditis* with *acute bacterial endocarditis* rather than with *subacute bacterial endocarditis*. On page 109, in a discussion of gallop rhythm, the author states that the mesodiastolic type occurs "between the first and second heart tones." This obviously was meant to be "between the second and first heart tones." The author's effort to explain the preponderance of coronary thrombosis in males as compared with females seems a bit too theoretical. He believes that coronary sclerosis and thrombosis represent a metabolic disturbance in which the blood lipoids are increased. He argues further that the female is better able to cope with increased blood lipoids than the male, since she adequately stores and handles physiological increases in blood lipoids during pregnancy.

This book does not assume the exhaustive scope or character of a textbook, but could be used beneficially by the medical student and busy practitioner as a practical companion to a cardiology text. The style is concise and forceful. The lucid manner of presentation promotes easy reading.

E T L

Infantile Paralysis—A Symposium Delivered at Vanderbilt University, April, 1941
239 pages, 23.5 × 16 cm National Foundation for Infantile Paralysis, Inc, New York City 1941 Price, \$1.25

This book is composed of six lectures delivered at Vanderbilt University in April of 1941 on the history, etiology, immunology, pathology and pathogenesis, epidemiology, and treatment of poliomyelitis, by Drs Paul F Clark, Charles Armstrong, Thomas M Rivers, Ernest W Goodpasture, John R Paul, and Frank R Ober. The purpose of this symposium has been to compile and evaluate the important publications on poliomyelitis and to serve as a stimulus and guide for further investigation.

Experimental studies on poliomyelitis have been limited due to the expense involved when working with monkeys. All other laboratory animals proved unsatisfactory. A possible solution to this problem is offered by the successful transfer of a strain of poliomyelitis virus from the monkey to cotton rats and then to white mice without loss of virulence. This method offers an opportunity for extensive investigation with minimal expense. The interpretation of results is beset with difficulties due to the presence of different strains of poliomyelitis virus. There are also the hazards involved when trying to apply data derived from animals to the human disease.

There is a conflict of opinion concerning the protective antibodies present in the blood serum of many persons who give no history of having had poliomyelitis. Some feel that they are of a nonspecific character, whereas others contend that they result from subclinical infections. It is of interest to note that in some instances the neutralizing antibodies do not appear in the blood until long after recovery from the disease, and that the paralytic form of poliomyelitis may develop even though neutralizing antibodies are present in the blood serum.

There is a difference of opinion as to the mode of transmission of the disease. The concept of neuron transmission is based upon work done using the *Macaca rhesus*. The virus was found to pass from the nares along the olfactory nerves to the olfactory bulb and then along the olfactory tract to the brain. Recent work with the *Macaca cynomolgus* reveals that this species is susceptible to intestinal inoculation. The virus has been found in the stools of active cases, recovered cases, and contacts. The virus is present in city sewage and has been found in water. The spread of the disease along waterways has been observed.

The reader will find in this book a stimulating survey of the established facts and unsettled problems of this interesting and in many respects baffling disease.

E F C

The Doctor and the Difficult Child By WILLIAM MOODIE, M.D., F.R.C.P., D.P.M.
214 pages, 21 × 14 cm. Commonwealth Fund, New York City. 1941. Price,
\$1.50.

This book is written in a simple, elementary fashion for the purpose of instruction in child guidance. It is fairly evenly divided into two main sections. The first has to do with instruction in the recognition of the problem, history taking, examination, and treatment. The second part deals with more specific problems of behavior, i.e., stealing, lying, feeding difficulties, nervousness, sex difficulties, etc.

Because of the variety of symptoms in behavior problems, no satisfactory system of classification or diagnosis will ever be possible. This difficulty in organization is noticeable throughout the book. It must once more be emphasized that the book fulfills its object in being elementary.

W M S

COLLEGE NEWS NOTES

GIFTS TO THE COLLEGE LIBRARY

We gratefully acknowledge receipt of the following gifts donated to the College Library of Publications by Members

Books

Dr Jacob Segal, F A C P, New York, N Y—"Diseases of the Respiratory Tract", Department of Experimental Medicine, George Washington University School of Medicine, Washington, D C—a bound volume of 32 reprints, many of which were written by members of the College

Reprints

Dr Frank N Allan, F A C P, Boston, Mass—1 reprint,
Dr Thomas W Baker, F A C P, Charlotte, N C—3 reprints,
Dr Edward G Billings, F A C P, Denver, Colo—1 reprint,
Dr L Minor Blackford, F A C P, Atlanta, Ga—2 reprints,
Dr Edward N Chapman, F A C P, Colorado Springs, Colo—1 reprint,
Dr Hyman I Goldstein (Associate), Camden, N J—2 reprints,
Dr Charles E Lyght, F A C P, Northfield, Minn—1 reprint,
Dr Robert C Page (Associate), Mount Vernon, N Y—2 reprints,
Dr R Henry Temple (Associate), Kinston, N C—1 reprint,
Dr J Lawn Thompson, Jr (Associate), Washington, D C—1 reprint

On September 10, 1941, Dr George R Herrmann, F A C P, Galveston, Tex, addressed the Sociedad Mexicana de Cardiologia at Mexico City, D F, on the subject of "The Blood and the Kidney in the Maintenance of Circulatory Equilibrium," reporting work done with Dr George M Decherd, Jr, F A C P, Galveston, Tex, and D B Calvin, Ph D

Dr Ignacio Chavez, F A C P, Mexico City, D F, presided Dr Francisco de P Miranda, F A C P, College Governor for Mexico, interpreted and discussed the paper

Dr Burton L Zohman, F A C P, has been promoted from Associate in Medicine to Assistant Clinical Professor of Medicine at the Long Island College of Medicine, Brooklyn, N Y

Captain Frederick L McDaniel, F A C P, (MC) U S N, has been appointed executive officer of the U S Naval Hospital at Great Lakes, Ill

Captain McDaniel has been a member of the Medical Corps of the U S Navy since 1917 During the first World War he was on duty with U S destroyers operating in European waters, and, following the cessation of hostilities in 1918, saw service in the West Indies, Washington, D C, and with the Pacific Fleet

On September 4, 1941, Dr Beirnard I Comroe, F A C P, Philadelphia, Pa, addressed the American Congress of Physical Therapy in Washington, D C, on "Physical Therapy in Arthritis"

The Association of Military Surgeons of the United States will hold its annual meeting in Louisville, Ky, October 29 to November 1, 1941. This meeting will be a most timely and interesting one. War medicine and surgery have changed considerably since the previous emergency. Mechanization of armies and air bombardments have created new and difficult problems.

All members of the medical profession are invited to attend as guests, for there will be something of special interest to everyone.

The following members of the College will present papers at this meeting: Rear Admiral Ross T. McIntire, F A C P, Surgeon General, U S Navy, Major Frank B. Wakeman (Associate), (MC) U S A, representing Major General James C. Magee, F A C P, Surgeon General, U S Army, Major General Charles R. Reynolds, F A C P (MC) U S A, Retired, Harrisburg, Pa., and Colonel Leonard G. Rowntree, F A C P, (MRC) U S A. General Reynolds is chairman of the program committee.

During June the Florida Medical Association and the Florida State Board of Health sponsored their 9th annual series of postgraduate courses for physicians, at Jacksonville, Fla. Among the members of the College who conducted these courses were:

Dr. Henry M. Thomas, Jr., F A C P, Baltimore, Md.—Medicine,
Dr. Charles F. Mohr (Associate), Baltimore, Md.—Venereal Diseases,
Col. Luther R. Poust, F A C P, (MC) U S A—Military Medicine,
Comdr. Eben E. Smith, F A C P, (MC) U S N—Military Medicine

Dr. Harry L. Alexander, F A C P, has been promoted to Professor of Clinical Medicine at Washington University School of Medicine, St. Louis, Mo. He has also been appointed Acting Head of the Department of Internal Medicine at the University, succeeding Dr. David P. Barr, F A C P, who resigned to accept an appointment as Professor of Medicine at Cornell University Medical College, New York, N. Y.

The Oregon State Medical Society held its 67th Annual Session and Post-graduate Assembly in Portland, September 3-6, 1941. Among the members of the College who spoke at this meeting were:

Dr. Milton B. Cohen, F A C P, Cleveland, Ohio—"Nature of Allergy, Its Pathology and Mechanisms of Its Production," "Management of Patients with Asthma, Hay Fever and Other Allergic States," and "Growth Disturbances Produced by Allergy",

Dr. Henry J. Tumen (Associate), Philadelphia, Pa—"Diagnosis and Treatment of Jaundice," "Management of Patient with Irritable Colon," and "Clinical and Gastroscopic Features of Chronic Gastritis"

Dr. M. Herbert Barker, F A C P, Chicago, Ill., spoke on "Chemotherapy—Sulfonamide Group," and Dr. Harold Feil, F A C P, Cleveland, Ohio, spoke on "Cardio-vascular Disabilities of Railway Employees—Problems of the Consultant. A Review of Eight Years' Experience" at the 52nd Annual Meeting of the American Association of Railway Surgeons, held in Chicago, Ill., September 8-10, 1941.

The second triennial reunion for alumni of the University of Michigan Medical School and former staff members and house officers of the University Hospital was

held in Ann Arbor, Mich, October 2-4, 1941 Among the alumni speakers who are members of the College were

Dr Charles L Brown, F A C P, Philadelphia, Pa—"Clinical Aspects of Osteoporosis",

Lt Col Joseph R Darnall, F A C P, (MC) U S A—"Concerning Army Medical Service",

Dr Robert T Monroe, F A C P, Boston, Mass—"Old Age",

Dr Walter M Simpson, F A C P, Dayton, Ohio—"New Developments in the Diagnosis and Treatment of Brucellosis"

The 7th Annual Piedmont Post Graduate Clinical Assembly was held at the Anderson County Hospital, Anderson, S C, September 9-11, 1941 Among the members of the College who spoke at this meeting were

Dr Franklin B Peck (Associate), Indianapolis, Ind—"Therapeutic Application of the Various Insulins",

Lieut Col Elias E Cooley, F A C P, (MC) U S A—"Medico-military Problems of the Moment",

Dr Kenneth M Lynch, F A C P, Charleston, S C—"Pathology of Uterine Carcinoma",

Dr H Sheridan Baketel, F A C P, Jersey City, N J—"The Future Economic Status of the Physician",

Dr William deB MacNider, F A C P, Chapel Hill, N. C—"The Sick Individual as a Biological Problem"

The 4th Institute on Postgraduate Psychiatric Education for State Hospitals held under the auspices of the American Psychiatric Association was held at the Western State Hospital, Fort Steilacoom, Wash, September 1-13, 1941 Dr Walter Freeman, F A C P, Washington, D C, and Drs Frederick Lemere (Associate) and Edward D Hoedemaker, F A C P, Seattle, Wash, were among those who conducted the course, which included lectures and clinics

Among the guest speakers at the 100th Annual Meeting of the State Medical Society of Wisconsin, held in Madison, September 10-12, 1941, were

Dr Henry W F Woltman, F A C P, Rochester, Minn—"Late Neurologic Manifestations in Cases of Injury",

Dr James A Evans, F A C P, Boston, Mass—"Cardiac Accidents and Their Management",

Dr Philip S Hench, F A C P, Rochester, Minn—"Classification and Management of Rheumatoid Disease",

Dr John W Towey, F A C P, Powers, Mich—"How Early Tuberculosis Can Be Detected in the Office"

Dr Nathan B Van Etten, F A C P, New York, N Y, spoke on "The Triumphs of Optimism" at the centennial dinner held during this meeting

Dr Carlo J Tripoli, F A C P, Assistant Professor of Medicine at Louisiana State University School of Medicine, New Orleans, has been appointed Director of the newly created Helis Institute for Medical Research This Institute expects to establish various clinical and experimental divisions at medical schools and hospitals, the first of which has already been organized as the Center of Research of Hotel Dieu Hospital

The Michigan State Medical Society held its 76th Annual Meeting at Grand Rapids, September 16-19, 1941. Among the speakers were

Dr Russell L Cecil, F A C P, New York, N Y—"Arthritis—A Curable Disease",

Dr Francis E Seneear, F A C P, Chicago, Ill—"Serologic Aspects of Syphilis",

Dr Lawrence Kolb, F A C P, Washington, D C—"The Needs and Possibilities of Research in Mental Disease",

Dr Charles E Lyght, F A C P, Northfield, Minn—"Some Educational Aspects of Diagnosing Tuberculosis Early",

Dr Virgil P Sydenstricker, F A C P, Augusta, Ga—"Factors in Deficiency Disease",

Dr Chester S Keefer, F A C P, Boston, Mass—"Recent Advances in Chemotherapy of Infectious Diseases",

Dr Arlie R. Barnes, F A C P, Rochester, Minn—"Problems in the Differential Diagnosis of Coronary Artery Disease",

Dr Charles A Doan, F A C P, Columbus, Ohio—"Relationship of the Reticulo-endothelial System to Cellular and Humoral Immunity"

Among the speakers at the 19th Annual Fall Clinical Conference of the Kansas City Southwest Clinical Society, held in Kansas City, Mo, October 6-9, 1941, were the following members of the College

Dr Sara M Jordan, F A C P, Boston, Mass—"Medical Management of Peptic Ulcer",

Dr Ernest Perry McCullagh, F A C P, Cleveland, Ohio—"Clinical Use of Testicular Hormones",

Dr John T Murphy, F A C P, Toledo, Ohio—"X-Ray Treatment of Cancer of the Skin",

Dr Roy W Scott, F A C P, Cleveland, Ohio—"The Part Played by Age, Cardiac Hypertrophy and Coronary Arterial Change in Heart Failure"

Dr Charles T Stone, F A C P, Galveston, Tex, spoke on "Newer Aspects of Pneumonia" and Dr Oliver C Melson, F A C P, Little Rock, Ark, spoke on "Treatment of Hypertension" at the meeting of the Tri-State Medical Society (Louisiana, Texas and Arkansas), held in El Dorado, Ark, September 23-24, 1941

Among the guest speakers at the 71st Annual Session of the Colorado State Medical Society held in Estes Park, September 17-20, 1941, were

Dr Louis E Viko, F A C P, Salt Lake City, Utah—"Evaluation of Chest Pain",

Dr Elmer L Sevringhaus, F A C P, Madison, Wis—"Pituitary Therapy in General Practice, Treatment of the Menopause"

The 1941 Scientific Assembly of the Medical Society of the District of Columbia was held in Washington, September 30-October 2, 1941. Among the speakers were

Dr Soma Weiss, F A C P, Boston, Mass—"Pre-eclamptic and Eclamptic Toxemia in Pregnancy",

Dr Thomas Fitz-Hugh, Jr, F A C P, Philadelphia, Pa—"Differentiation of Anemias",

Dr Oscar B Hunter, F A C P, Washington, D C—"Newer Laboratory Procedures in the Diagnosis of Obscure Fevers",

Dr Wendell S Muncie, F A C P, Baltimore, Md—"Why Are There so many Neurotics?",

Rear Admiral Ross T McIntire, F A C P, (MC) U S N—"Aviation Medicine in the Navy",

Major General James C Magee, F A C P, (MC) U S A—"Care and Evacuation of Battle Casualties in Modern War",

Lieut Comdr Lloyd R Newhouser, F A C P, (MC) U S N—"Use of Blood Substitutes by the Armed Forces",

Col Leonard G Rowntree, F A C P—"Health of the Nation as Revealed by Selective Service"

Among the guest speakers at the 92nd Annual Session of the Indiana State Medical Association, held in Indianapolis, September 23-25, 1941, were

Dr Louis Hopewell Bauer, F A C P, Hempstead, N Y—"Aviation Medicine",

Dr James P Leake, F A C P, U S Public Health Service—"Poliomyelitis",

Dr Ralph Pemberton, F A C P, Philadelphia, Pa—"Arthritis",

Dr Russell L Haden, F A C P, Cleveland, Ohio—"More Common Blood Dyscrasias Seen by the General Practitioner",

Dr Fred M Smith, F A C P, Iowa City, Iowa—"Management of the Patient with Coronary Disease"

Dr James O Ritchey, F A C P, Indianapolis, was chairman of a panel discussion on "The Clinical Application of the Newer Laboratory Procedures as Pertains to the Man in General Practice"

Dr Archibald H Beard, F A C P, and Dr Samuel A Weisman, F A C P, have been promoted to Clinical Associate Professors of Medicine at the University of Minnesota Medical School, Minneapolis

Under the presidency of Dr Walter B Martin, F A C P, Norfolk, the Medical Society of Virginia held its annual meeting at Virginia Beach, October 6-8, 1941. Comdr Waddie P Jackson, (MC) U S N R (Associate), Norfolk, spoke on "The Airplane, a Possible Means of Transmission of Disease," and Dr Louis Hamman, F A C P, Baltimore, Md, conducted a clinical pathologic conference

The Scientific Society of San Antonio (Texas) recently presented the Franklin Medal to Col Charles F Craig (MC) U S A, Retired, F A C P, San Antonio, for distinguished work in science. Colonel Craig is the first recipient of this medal, which was donated by Colonel and Mrs W Lee Hart of San Antonio and named in honor of the late Dr Thomas H Franklin

The Philadelphia County Medical Society held its inaugural meeting September 17, 1941. At this meeting Dr Louis H Clerf, F A C P, was installed as President of the Society, succeeding Dr Edward L Bortz, F A C P, College Governor for Eastern Pennsylvania

Dr Louis Faugeres Bishop, Jr gave a talk on "The Senile Heart" at the Sixth Harlow Brooks Memorial Clinical Conference at the Sage Memorial Hospital, Ganado, Arizona, August 25, 1941. He also delivered the Commencement Address on "Harlow Brooks" to the graduating class of the Sage Memorial Hospital School

Dr Joseph H Barach, Pittsburgh, Pa , addressed the Jefferson County Medical Society at Punxsatawny, Pa on September 11, 1941 His subject was "Present Day Treatment of Diabetes and Its Complications"

DR WALTER REECE BERRYHILL ELECTED DEAN OF THE UNIVERSITY OF NORTH
CAROLINA SCHOOL OF MEDICINE

Announcement was made September 9 that Dr Walter Reece Berryhill, F A C P , had been elected Dean of the School of Medicine and Chairman of a newly-created division of medical sciences of the University of North Carolina, the election having been made by the Executive Committee of the Board of Trustees

Dr Berryhill graduated from Harvard Medical School in 1927, and had been acting dean of the School of Medicine of the University of North Carolina since the resignation a year ago of Dr W DeB MacNider, F A C P , who, after overseeing the construction of the school's new home, resigned to return to laboratory and classroom work Dr Berryhill is also to head the new division of medical sciences which will include the School of Medicine, the School of Public Health, the County Health Service and the University Health Service It is said the purpose of the new division is to correlate and strengthen the various activities in the medical field at the University

Dr Berryhill is a native of Charlotte, North Carolina, where he was born in 1900 He attended the Charlotte schools and entered the University of North Carolina, receiving his A B degree in 1921 He distinguished himself as an undergraduate and was class president and head of the student council during his senior year He returned to the University in 1923 and enrolled in the Medical School, but later transferred to Harvard Medical School from which he graduated in 1927 He served as intern and resident physician in Boston City Hospital and at Lakeside Hospital in Cleveland from 1927 to 1930, and from 1930 to 1933 was instructor in medicine and attending physician at Lakeside Hospital He returned to the University of North Carolina in 1933 as university physician and rapidly advanced to associate professor in medicine, assistant dean and acting dean of the Medical School, culminating in his present appointment as Dean

OBITUARIES

DR ALLEN KRAMER KRAUSE

On May 12, 1941, after several years of serious illness, Dr Allen Kramer Krause died in Providence, Rhode Island at the age of 60 years

He was born in 1881 in Lebanon, Pennsylvania and was graduated from Brown University in 1901, receiving his A M degree from the same university in 1902. He received the degree of M D from Johns Hopkins University in 1907 and, except for a brief period during which he was Assistant Director of the Saranac Laboratory, subsequently was an active member of the Johns Hopkins Faculty for nearly 20 years, first as Instructor in Pathology, later as Associate Professor of Medicine, Director of the Kenneth Dows Tuberculosis Research Laboratories, Associate Physician, Johns Hopkins Hospital and Physician-in-Charge of the Phipps Tuberculosis Dispensary. When he left Baltimore in 1929 to take charge of the Desert Sanatorium in Tucson, Arizona, he was made Visiting Lecturer in Medicine at Johns Hopkins University. While he was in the south west, Stanford University appointed him (1929) Clinical Professor of Medicine and in 1932 the University of Southern California conferred the same honor upon him.

He was an active member of many scientific societies, too numerous to detail. He was an honorary member of the Harvey Society, the Interurban Clinical Club, the American Society of Clinical Investigation and the Los Angeles Clinical and Pathological Society.

During the first five years of its existence, that is, from 1917 to 1922, he was Managing Editor of the *American Review of Tuberculosis* and subsequently, Editor. He was Editor of the American Section of the British journal *Tubercle* and on the Editorial Board of a number of other important foreign medical journals. He was the author of articles on tuberculosis in the *Encyclopedia Britannica*, Nelson's *Loose Leaf System of Medicine*, Osler's *Modern Medicine*, Piersol's *Cyclopedia of Medicine* and Cecil's *Text-Book of Medicine*.

In 1931 he was the recipient of the Trudeau Medal of the National Tuberculosis Association. In American Men of Science he was "starred."

Allen Krause had a brilliant mind in a too frail body. Tuberculosis which troubled him early after graduation at Johns Hopkins never really laid him low. This brief illness seemed only to stimulate his interest in the historical, clinical, experimental and public health aspects of the disease. It led to his important studies on allergy and immunity, to his editorial opportunities, to his official positions in the Phipps Dispensary at Johns Hopkins and finally to his migration to the south west. It led to his voluminous writings and innumerable addresses all over the United States. He read everything and seemed to remember everything he read. He spoke with great fluency and assurance to both laymen and the medical profession.

Through his editorial efforts the *American Review of Tuberculosis* rapidly assumed and has maintained a leading place in its field. As Editor, Allen Krause had the opportunity which he generously utilized to encourage much experimental work in tuberculosis in American laboratories. In every city he had a host of devoted admirers, who flocked to hear his formal addresses and pursued him afterwards to his hotel room where he loved to "hold forth" until the small hours of the morning. The volume of work, editorial and other writing which he did was enormous. The rapidity with which he did it and its accuracy, clarity and fluency were phenomenal.

Tragedy tortured his last few years but the record of his brilliant life is unique in American medicine.

JAMES J. WARING, M.D., F.A.C.P.,
Governor for Colorado

DR. HENRY JOACHIM

Dr. Henry Joachim died at his residence in the Waldorf Astoria Towers in New York City, on August 18, 1941, of carcinoma of the cecum, having made his own diagnosis prior to the time of examination by his colleagues.

Dr. Joachim was born in Brooklyn, on April 16, 1883, and his professional activities were both in New York City and Brooklyn. He received his medical degree from Cornell University in 1904 and then had postgraduate study at the Allgemeine Krankenhaus, Vienna, and at the University of Prague, 1905-06-07. Following his return to the United States, he started his practice in Brooklyn and became an Associate in Medicine at the Brooklyn Jewish Hospital from 1911-1923. During this time he was made Instructor in Histology and Bacteriology at the Long Island Medical College and in 1918 he became the head of the department of Gastroenterology and Clinical Professor of Medicine, serving until 1931. During this time he was Attending in Medicine at St. Catherine's Hospital, 1916-1923, Chief in Medicine, Greenpoint Hospital 1918-1923, Attending in Medicine, Long Island College Hospital, 1918-1932. At the time of his death he was Director of Medicine, Cumberland Hospital, Chief of Medicine, Beth-Moses and Israel-Zion Hospitals, Jewish Sanitarium and Hospital for Chronic Diseases, Chief of Medicine, Sydenham Hospital, New York City. He was a member of the State Industrial Council and past president of the Medical Society of the County of Kings and the Brooklyn Academy of Medicine, Fellow of the New York Academy of Medicine, the American Medical Association, and a Fellow of the American College of Physicians since 1920. He was author of a host of published articles in leading medical journals, and of "Practical Diagnosis and Treatment" (Charles Thomas Company, 1940).

Dr. Joachim was an inspiring teacher and a keen diagnostician. It was for these reasons that his ward rounds and clinics always attracted a large audience. The outstanding traits of Dr. Joachim's character were his re-

markable encyclopedic memory, his scientific acumen, and, above all, his gentleness of character. He was highly respected and admired by all who had the privilege of contact with him.

C F TENNEY, M D , F A C P ,
Governor for Eastern New York

DR ISADORE KAUFMAN

On August 11, 1941, medicine lost an active and interested member with the death of Dr. Isadore Kaufman.

Dr. Kaufman was born in Charlottesville, Virginia on April 21, 1882. He attended the University of Virginia, where he obtained his M D degree in 1904. He served a one year internship at Mt. Sinai Hospital in New York.

Being primarily interested in tuberculosis he gave generously of his time and efforts for that cause. Dr. Kaufman was Visiting Physician at White Haven Sanatorium from 1911 until the time of his death. He was also Medical Director of Kensington Dispensary for Tuberculosis since 1918 and Consultant in Pulmonary Diseases at the Abington Memorial Hospital.

For many years Dr. Kaufman was a lecturer in Physical Diagnosis and served as Head of the Department of Physical Diagnosis at the University of Pennsylvania School of Medicine. He was actively identified with the Henry Phipps Institute, having served as Clinician and Associate Clinical and Sociological Director in former years.

In addition to an already full schedule, Dr. Kaufman was the author of several published articles. He was a Fellow of The American College of Physicians since 1929, a member of The Philadelphia County Medical Society, a member of The National Tuberculosis Association, a Fellow of The American Medical Association, and a member of The Medical Society of The State of Pennsylvania.

With so much to contribute to the medical profession, and with a fine personality, Dr. Kaufman was held in high esteem by his colleagues and friends. It is therefore with deep regret that we write of his death.

EDWARD L. BORTZ, M D , F A C P ,
Governor for Eastern Pennsylvania

DR WILLIAM BERNARD KINLAW

Dr. William Bernard Kinlaw of Rocky Mount, N C , was killed on July 24, 1941, in an automobile accident. He was born July 17, 1896, the son of Mr. and Mrs. H. R. Kinlaw of Rocky Mount.

After graduation from the high school of his native city, he attended the University of North Carolina, and graduated in medicine from the University of Pennsylvania in 1920. After two years' internship in the Episcopal Hospital of Philadelphia, he returned to his home city, where he spent a year

in general practice, after which he was associated in 1923-24 with Dr P P McCam of the State Sanatorium. He then decided to devote himself entirely to internal medicine, and became attending physician to the Park View Hospital of Rocky Mount, and later the Memorial Hospital of Kinston. In 1939 and 1940 he practiced in Binghamton and Elmira, N Y, returning to Rocky Mount in January, 1941.

His published material showed his more intense interest in pulmonary and cardiac conditions, though his bibliography includes such conditions as reports on Brill's disease, post vaccinal encephalitis, and effort syndrome.

He was a member of his local and state medical societies, of the Seaboard Medical Society, the Tri-State Medical Society, the American Medical Association, and became a Fellow of the American College of Physicians in 1929.

In 1923 he married Miss Dorothy Wisner of Philadelphia, Pa, who, with one son, W B Kinlaw, Jr, survives.

Dr Kinlaw was a man of exceptionally attractive personality and great charm, his untoward death at the age of forty-five leaves a void in the affections of a great many of the profession who were privileged to know him well.

CHARLES H COCKE, M D, F A C P,
Governor for North Carolina

DR WILLIAM HENRY WILSON

Dr William Henry Wilson died at his home in Joliet, Ill, on May 15, 1941, at the age of seventy-four. Death resulted from cerebral thrombosis. Dr Wilson was born near Brockville, Ont, Canada, on October 26, 1866. As a boy of seven he moved with his family to Benton County, Iowa. In 1893 he graduated from the University of Michigan. In common with many other ambitious young men, he began his first work as a teacher in the high school at Fort Smith, Ark, in the same year. In 1898 he received his medical degree from the Hahneman College at Chicago, Ill.

During the course of his long attachment to Hahnemann College, Dr Wilson served as pathologist from 1900-1923, and from 1919-1923 he was registrar. In 1923, with the termination of the Hahnemann Medical College as an active teaching center, he moved to Joliet, and for the next 15 years he was pathologist at the Silver Cross Hospital. From 1903-1904 he was pathologist at Cook County Hospital.

Dr Wilson was a Fellow (1923) of the American College of Physicians, a member of the American Medical Association, the American Society of Clinical Pathologists, the American Association for the Study of Neoplastic Diseases and the Will County Medical Society. He was a Mason, a Shriner, an active member of the Rotary Club in Joliet, a member of the alumni chapter of Sigma Alpha Epsilon and Phi Rho Epsilon. He was formerly vice-chairman of the consulting committee of the Chicago Department of

Health and a member of the Medical Reserve Corps of the United States Army. He is survived by his widow and two daughters.

Dr. Wilson was interested in nature study and in geology. He became particularly familiar with the interesting geological features around Joliet and Will County. He was an active participant in the efforts to extend the forest preserve system of Will County. Dr. Wilson was always deeply interested in opera and was recognized as an authority. At all times those who knew him recognized in him an educated physician and gentleman, whose alertness and general knowledge made him an interesting companion and friend.

LEROY H. SLOAN, M.D., F.A.C.P.,
Governor for Northern Illinois

DR. WILLIAM HURLEY STRIETMANN

Dr. William Hurley Strietmann, F.A.C.P., of Oakland, California, died on July 14, 1941. Death came suddenly while he was at his office, and was due to coronary artery disease.

Dr. Strietmann was born in Cincinnati, Ohio, November 8, 1880. He graduated from the University of Cincinnati College of Medicine in 1905 and went abroad for postgraduate work in Vienna from 1906 to 1907. He was appointed Instructor in Bacteriology at his Alma Mater in 1907. From 1908 to 1911 he was assistant in Physiology. In 1912 he was appointed Professor of Physiology at the Oakland College of Medicine, Oakland, California, and in 1916 he was made Associate Professor of Medicine. For several years he was Chief of the Medical Service at the Alameda County Hospital. He was a member of the Alameda County Institutions Commission, a member and past president of the Alameda County Medical Society; also member and past vice-president of the California State Medical Association. He was a Fellow of the American Medical Association and a Fellow of the American College of Physicians since 1917.

Dr. Strietmann was one of the first in Oakland to confine himself to Internal Medicine. He had a large consulting practice, but gave freely of his time and energy to the Alameda Institutions Commission and to the Alameda County Hospital, as physician-in-chief.

Two daughters and a son survive, but Mrs. Strietmann passed away about one year ago.

Dr. Strietmann's work is finished, but his influence will be felt among his patients and fellow physicians for long into the future.

ERNEST H. FALCONER, M.D., F.A.C.P.,
Governor for Northern California

TOLDT'S **ATLAS OF HUMAN ANATOMY**

Now reissued with improved paper, printing, and binding

Unsurpassed in

Accuracy
Completeness
Abundance of
Illustration
(1505 figures)

It is printed from American-owned plates and will therefore always be available in this country

THIS ATLAS has long been noted for its extraordinarily accurate and exhaustive pictorial representation of all the parts of the human anatomy. There are, for instance, 26 views of the temporal bone alone. All illustrations are line drawings, which give maximum accuracy of detail in reproduction. These are printed in from one to five colors, adding visual emphasis to clarity of design.

"The illustrations are exquisitely executed, many of them in colours, with a wealth of detail which can only be fully appreciated by actually studying them."

—LONDON MEDICAL TIMES

2 vols. 956 pp + appendix and indices
The set, \$10 00

"**As OSLER** has been the standard medicine

Da Costa the authoritative surgery

TOLDT has become the recognized atlas on human anatomy . . . "

—Archives of Physical Therapy

"**T**HE special advantages of this atlas consist in the large number of illustrations, in the inclusion among them of a few skillfully designed diagrams indicating general principles of structure and development, and in the extraordinary completeness with which the essential facts of structure have been shown in the preparations and drawings."

—JNL A.M.A.

60 Fifth Avenue

MACMILLAN

New York City

Please Mention this Journal when writing to Advertisers

TRAUMA AND DISEASE

Edited by

LEOPOLD BRAHDY, B.S., M.D.

Physician in Charge of Occupational Diseases
and Injuries in the Office of the Corpora-
tion Counsel of the City of
New York

and **SAMUEL KAHN, B.S., M.D.**

Medical Examiner in the Bureau of Work-
men's Compensation of the Department
of Labor, State of New York,
New York City

NEW (2D) EDITION

Octavo, 655 pages, illustrated

Cloth, \$7 50, net

This is a composite work in contri-
butions by twenty-four distinguished
specialists, each of whom points out
the relationship between trauma and
diseases. The book supplies a sound,
scientific basis for determining to what
extent an injury may be the cause of
a disease or how far it may aggravate
a disease existing previous to the in-
jury. The rise of accident rates, the
increase of compensation laws and the
growth of industrial medicine make a
work of this character necessary.

This book assembles in a single vol-
ume widely scattered literature on this
subject and covers every phase that
must be considered in determining the
traumatic origin of disease.

Washington Square

LEA & FEBIGER

Philadelphia, Pa.

Theocalcin - - *prescribed with or without digitalis*

Combinations of Theocalcin and digitalis are frequently prescribed to improve cardiac function in congestive heart failure. In other cases, when digitalis fails to give relief, Theocalcin in doses of 1 to 3 tablets t.i.d. is often effective.

Theocalcin is a well tolerated diuretic and myocardial stimulant which acts promptly to reduce edema, diminish dyspnoea and strengthen heart muscle.

Theocalcin is available in 7½ grain tablets and in powder form.



Theocalcin, brand of theobromine-calcium salicylate
Patent and Trade Mark Reg U S Pat Off

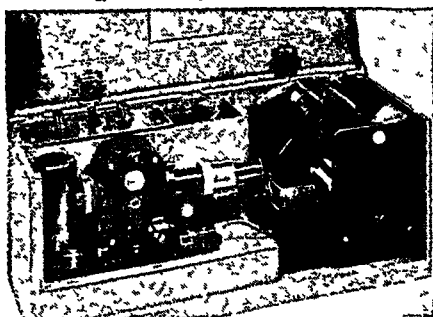
BILHUBER-KNOLL CORP. ORANGE, NEW JERSEY.

Hand Polished TOOTH BY TOOTH



The acknowledged accuracy of
Cambridge Records is the result
of extreme care in manufacture

THE "SIMPLI-TROL" PORTABLE MODEL is contained in one case 8" x 10" x 19" and weighs but 30 pounds. Mobile and Stationary models also available for Hospital and Clinical use. All models may be had for straight electrocardiography or with heart sound recording. Send for literature.



THE WORK of the best available gear cutting machines does not meet the exacting standards of Cambridge for finished parts to be used in our Electrocardiograph.

In this precision shop, a skilled instrument maker polishes each gear, tooth by tooth, evening-off minute irregularities that can only be seen with a glass. Then the gears are meshed and run. If the slightest sound or vibration is detected, even with an amplifying instrument, the spot is marked and the gears repolished until practical perfection is attained.

Thus the hidden values of the Cambridge Electrocardiograph are the result of painstaking effort in every detail of building this fine instrument. The Cardiologist knows, either from experience or from reputation, of the accuracy of Cambridge Records. He rightfully assumes sound fundamental design. He can see and appreciate the convenient operating features but the qualities that daily increase his pride of ownership are the result of Cambridge precision craftsmanship.

CAMBRIDGE INSTRUMENT CO., Inc., 3730 Grand Central Terminal, New York
Pioneer Manufacturers of the Electrocardiograph

CAMBRIDGE

all-electric

ELECTROCARDIOGRAPH

BACK NUMBERS
of

MEDICAL PERIODICALS

SETS — VOLUMES — NUMBERS
FOREIGN AND AMERICAN

A stock of more than two million copies of 6,000 periodicals, yearbooks and proceedings enables us to fill 85% of all orders immediately and at reasonable prices.

SELL TO US

Send us lists of periodicals, particularly technical, scientific and scholarly, which you want to sell. Our stock needs constant replenishing and you may wish to sell just the ones we need most.

PERIODICALS CLEARING HOUSE

A DIVISION OF

THE H. W. WILSON COMPANY

950 University Avenue New York City

New LaMotte Outfit

for the Determination of

Sulfanilamide, Sulfapyridine,
Sulfathiazole, Sulfaguanidine and
Sulfadiazine in Blood and Urine

LATEST improved procedure employs N (1-Naphthyl) ethylene-diamine dihydrochloride and Ammonium Sulfamate in the coupling reaction. Determines free and combined form in blood and urine. This simple procedure enables one to determine one or all five of these drugs in a minimum amount of time. Outfit is complete with instructions. Price \$23.50 F.O.B. Towson, Baltimore, Md.



LaMotte Chemical Products Co.

Dept. C, Towson, Baltimore, Md.

Being made from the powdered leaves,
all that Digitalis can do

Pil. Digitalis (Davies, Rose) will do.

They are physiologically standardized



*A New Edition of a Book
Which Has Become a
Standard Classic*

DISEASES OF THE BLOOD

by
Roy R. Kracke, M.D.

54 Color Plates
and 46 Other
Illustrations

692 Pages

\$15

The second edition of this classic brings this comprehensive treatment of the field of hematology up to the minute. Five new chapters totaling a hundred pages have been added and the text in its entirety has been thoroughly revised.

This book contains everything known and every theory that has gained acceptance about the normal blood, as well as blood diseases, with complete diagrams, symptomatology, details of treatment, differential diagnosis and prognosis. More than 300 illustrations of individual cells in full color in 54 full pages of color plates of all known blood diseases are reproduced with such fidelity that even the minor variations show in the blood cells and in the bone marrow.

Internists everywhere acclaim Kracke's work as outstanding on the subject. Of the earlier edition, the *Annals of Internal Medicine* said, "A volume which will hold its own in competition with the numerous books on hematology," and this new, enlarged edition is a better, greater book in every way. Be sure your copy is ordered now.

A Comprehensive Survey of the Diagnosis and Treatment of

NUTRITIONAL DEFICIENCIES

by John B. Youmans, M.D., F.A.C.P.

Almost more than any other phase of our national health, nutritional deficiencies are receiving a major share of the attention of the press and, through the press, the public as a whole.

This book is designed to give the general practitioner a survey of the whole field, covering completely diagnosis and treatment of the deficiency diseases. There has been a rapid increase in our knowledge of these diseases but much of it has come through laboratory research—widely scattered and difficult of access.

This book brings together all the information necessary for the understanding and management of nutritional deficiencies *in practice*. It covers the field thoroughly—making it a book that *you* need—a book that will bring *your* knowledge of this much-discussed subject right up-to-the-minute. Send your order in today.

385 Pages • 16 Illustrations • Price \$5.00

J. B. LIPPINCOTT COMPANY

Philadelphia • London • Montreal



A PIONEER VITAMIN B COMPLEX

Dependable and Economical for Regular Use

Vitamin research in nutrition and medicine discovered the high vitamin B, then the vitamin B complex potency of Vegex. It is comparable with grain grown dried brewers yeast—the richest known source—in the whole of the vitamin B complex. Whatever the need or desire for high concentration, the natural vitamin B complex has not been concentrated into a more potent form than brewers yeast or Vegex, the autolyzed extract of brewers yeast.

The value of Vegex has been well established in the treatment of beriberi, pellagra (it is a rich, natural source of nicotinic acid), alcoholic polyneuritis, for supplying the B vitamins in lactation promotion and child growth. There have been over sixty published reports in medical literature on the successful use of Vegex for the extrinsic factor in the anemias.

Tasty Flavor—Easily Borne

Vegex has a meat-like flavor. It enhances the flavor of meat and vegetable dishes, soups, etc.

Vegex is so easily borne that it is regularly prescribed for infants, in post-operative cases as well as for general vitamin B complex reinforcement. It is particularly useful in liquid or other restricted diets.

Simple Uses

The tasty flavor of Vegex is best appreciated when it is used as directed—diluted and in small quantities. It is a condensed extract of brewers yeast and the flavor is concentrated.

Vegex may be added to the diet in a variety of ways, a few of which are as follows:

Vegex Bouillon

From one-half to a level teaspoonful of Vegex to a cup of hot water or the water in which vegetables were cooked.

Chilled Vegex

Add a dash of lemon to Vegex bouillon and thoroughly chill.

Vegex-Tomato Juice Cocktail

Dissolve from one-half to a level teaspoonful of Vegex in a little warm water and add to a glass of chilled tomato juice.

Vegex-Milk

Add one-half teaspoonful of Vegex to a cup of hot milk.

Vegex Butter

Cream together one part of Vegex with ten or twelve parts of butter for bread, toast or baked potatoes.

Vegex with Vegetables or Meats

After broiling, spread a little Vegex to taste on steaks, chops, mix with vegetables, macaroni, etc.

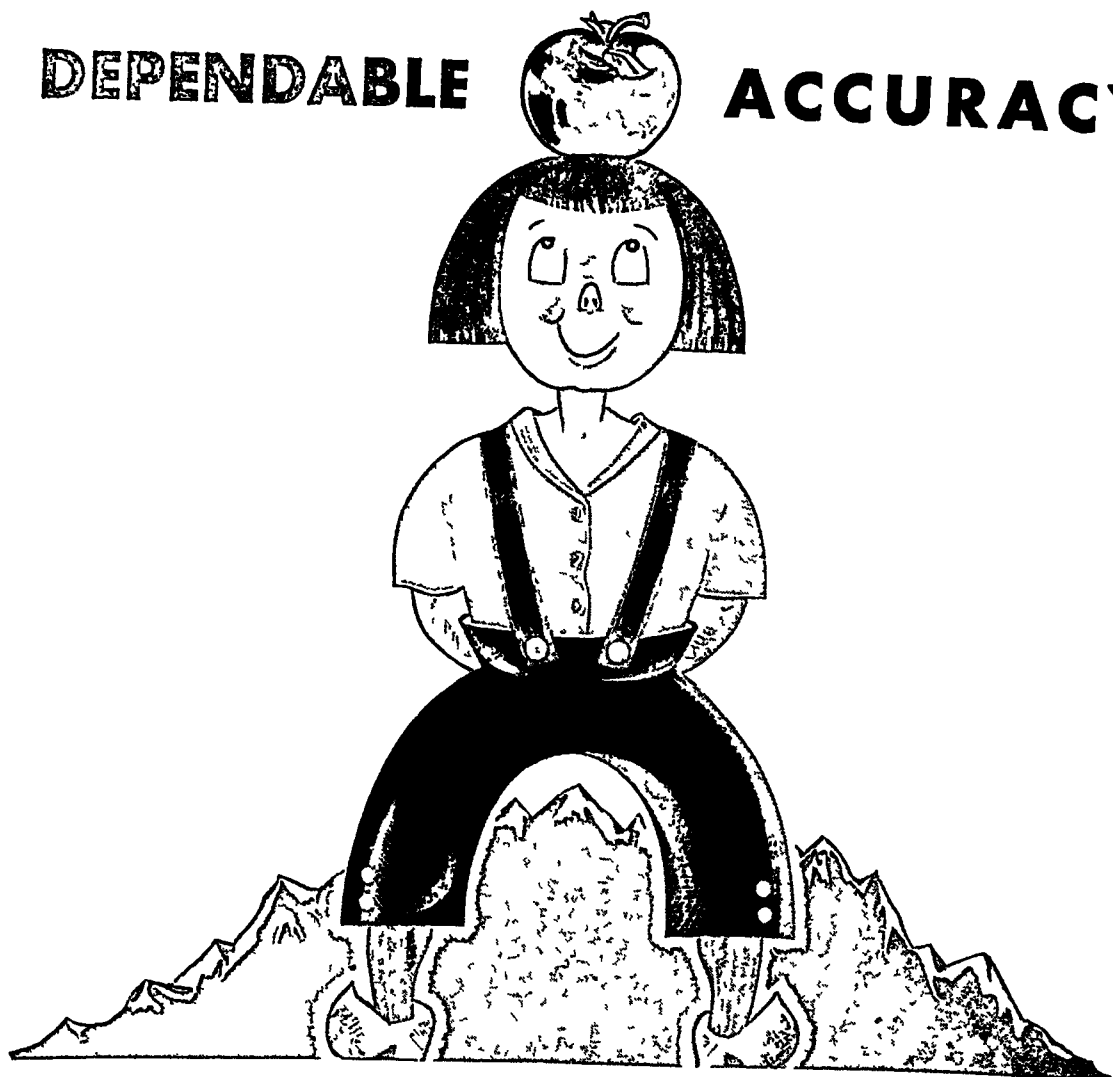
Samples for clinical or professional use will be sent on request

VITAMIN FOOD CO., INC. 122 Hudson Street NEW YORK, N. Y. **VEGEX, INCORPORATED**

Please Mention this Journal when writing to Advertisers

DEPENDABLE

ACCURACY



LEGEND has it that in Father William's skill with a bow, Junior Tell had great confidence—a confidence in accuracy that could have been no greater than that of G-E Electrocardiograph owners in the routine accuracy of the Model "B." For this precision instrument's exclusive, scientifically correct design assures exact records of the heart's action.

It records accurately the minute changes in the heart waves, including their higher frequency components. Its adequate response to all frequencies present in the wave assures accurate measurement of R-wave amplitude. And deflection time is constant

because variations in patient's resistance do not require adjustment of the galvanometer. Thus there is a welcome absence of intricate adjustments and compensatory manipulations—hence it is simple to operate.

Important, too, are such features as the G-E Ekg's sturdy, all steel construction for durability, and self-contained power supply to allow real portability. Thus, physically, there is present every element of a wise clinical investment, and at a price which makes it as sound from an economic standpoint. To prove this to your own satisfaction, see a demonstration in your office—address Dept. F311.



GENERAL ELECTRIC X-RAY CORPORATION

2012 JACKSON BOULEVARD

CHICAGO, ILLINOIS



*Physiologic
Basis of*
**DIURETIC
THERAPY**

When the glomerular and tubular functions of the kidneys become impaired, alterations in the mechanism of urinary secretion occur. Often there results

a retention of water with generalized edema. In such cases it is believed that Salyrgan-Theophylline lowers tubular reabsorption and thus permits the excretion of water and salt.

Salyrgan-Theophylline is extensively employed in the treatment of cardiac and cardiorenal edema as well as dropsy of nephrosis. It can usually be administered periodically without loss of potency.

Salyrgan-Theophylline is injected intravenously or intramuscularly.

**WINTHROP
CHEMICAL
COMPANY,
INC.**

*Pharmaceuticals of merit
for the physician*

**NEW YORK, N. Y.
WINDSOR, ONT.**



HOW SUPPLIED Salyrgan-Theophylline solution (containing 10% Salyrgan and 5% theophylline) is supplied in ampules of 1 cc., boxes of 5, 25 and 100, and in ampules of 2 cc., boxes of 10, 25 and 100

SALYRGAN - THEOPHYLLINE

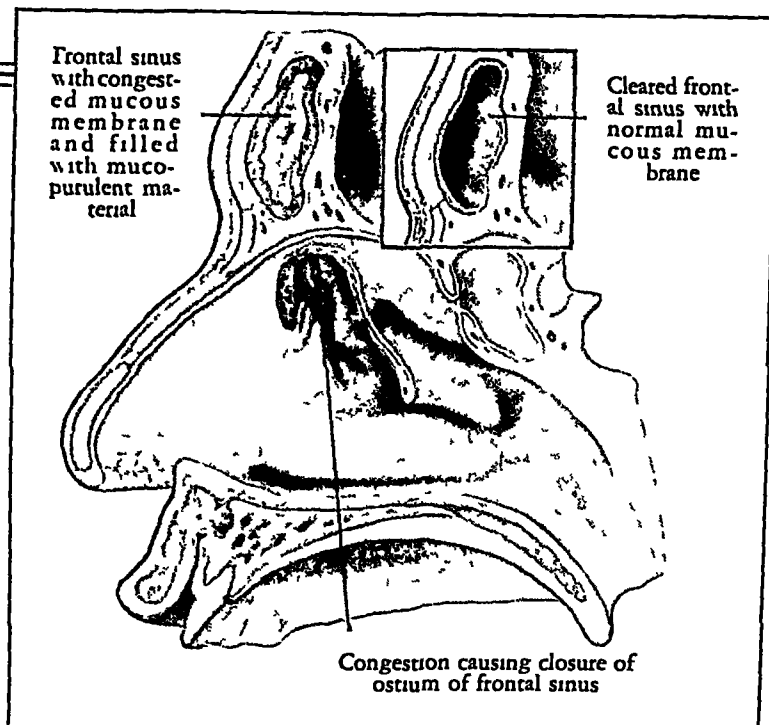
"Salyrgan," Trademark Reg U S Pat Off & Canada

(Mercury salicylallylamide-o-acetate of sodium with theophylline)

Brand of MERSALYL

*with
Theophylline*

PATHOLOGY OF THE UPPER RESPIRATORY TRACT



CATARRHAL INFLAMMATION OF THE FRONTAL SINUS

The above illustration demonstrates the route of infection to the frontal sinuses—demonstrates, too, the need for adequate drainage of the area. To shrink congested nasal mucous membranes quickly—to establish adequate drainage with more prolonged effect than ephedrine, may we recommend

NEO-SYNEPHRIN HYDROCHLORIDE

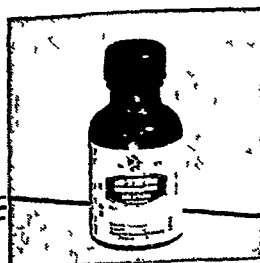
(laevo-alpha hydroxy beta methyl amino-3 hydroxy ethylbenzene hydrochloride)

DOSAGE FORMS.

SOLUTION— $\frac{1}{4}\%$ in saline solution ($\frac{1}{2}$ oz and 1 oz bottles)
 1% in saline solution ($\frac{1}{2}$ oz and 1 oz bottles)
 $\frac{1}{4}\%$ in Ringer's Solution with Aromatics ($\frac{1}{2}$ oz and 1 oz bottles)

EMULSION— $\frac{1}{4}\%$ low surface tension ($\frac{1}{2}$ oz and 1 oz bottles)

JELLY — $\frac{1}{4}\%$ in collapsible tube with applicator



SOLUTION



EMULSION



JELLY

FREDERICK STEARNS & COMPANY, Detroit, Michigan

New York

Kansas City

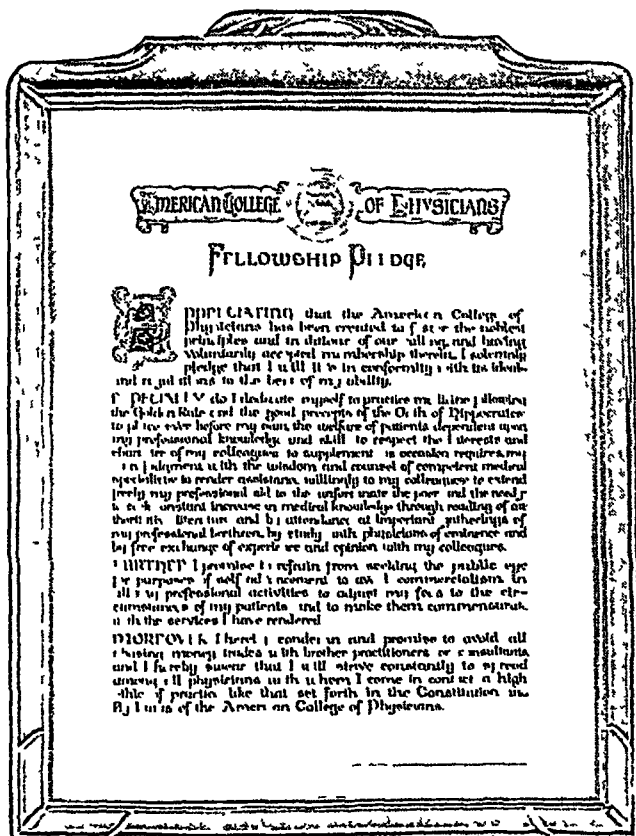
San Francisco

Windsor, Ontario

Sydney, Australia

Christmas Suggestions

FELLOWSHIP PLEDGE



Every Fellow of the American College of Physi- cians should display this Pledge in his office. It is beautifully engraved and bears the seal and colors of the College. For Fellows only.

Price, framed and delivered, \$5 00

FELLOWSHIP KEY

A charm bearing the seal of the American College of Physicians, wrought in solid gold and embossed in the College colors. For Fellows only

Price, delivered, \$7.00



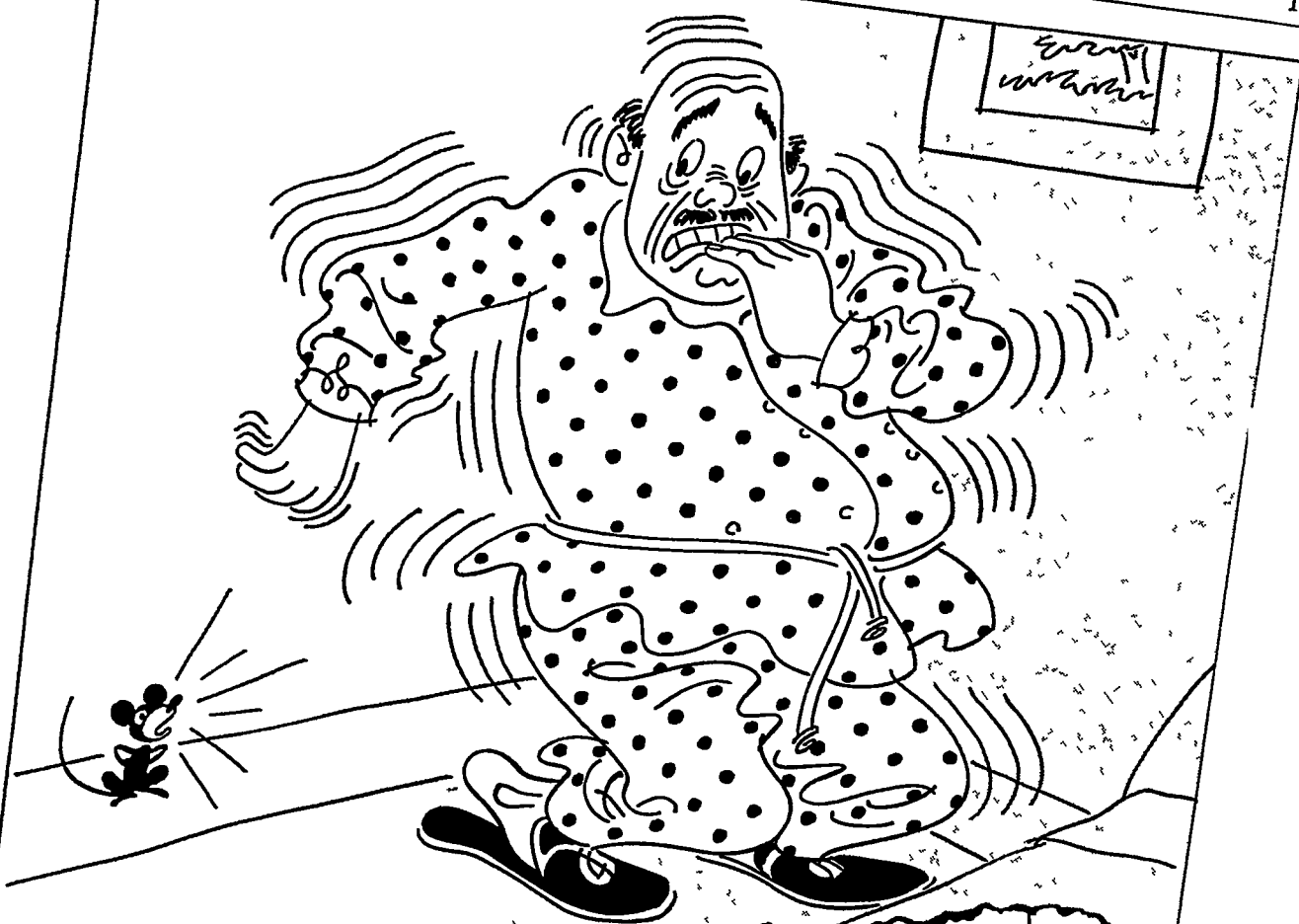
SUBSCRIPTION TO "ANNALS OF INTERNAL MEDICINE"

A suitable and stimulating gift for that doctor friend who is not a member of the College. Special Christmas Rate, \$6.00 per annum.

Send orders to

THE AMERICAN COLLEGE OF PHYSICIANS

4200 PINE STREET, PHILADELPHIA, PA.



★ ★ ★ Dear Doctor ★ ★ ★

DEAR DOCTOR:

My husband is nervous as a cat. The tiniest thing upsets him so He's supposed to be on a bland diet Is that what makes him so jumpy?

—MRS ROPESEND

DEAR MRS ROPESEND:

Lack of Vitamin B₁ often causes nervousness There is no reason why your husband can't have a bland diet and still increase his daily supply of Vitamin B₁. Just give him 5-Minute Cream of Wheat This delicious cereal—so simple to prepare—now con-

tains more calcium and phosphorus than the best whole wheat, and as much Vitamin B₁. It is also a very rich source of available iron * Yet it is extremely bland and fully digestible after only 5 minutes of cooking—even for babies. You'll be glad to know, too, that it costs less than a penny a serving.

—M. D.

*Every ounce of 5-Minute Cream of Wheat contains in average amounts 50 International Units of Vitamin B₁, 168 mg. of phosphorus, 143 mg. of calcium, 12 mg. of iron.

and phosphorus

ing—even for babies. You'll be

"Cream of Wheat" Reg U S Pat Off

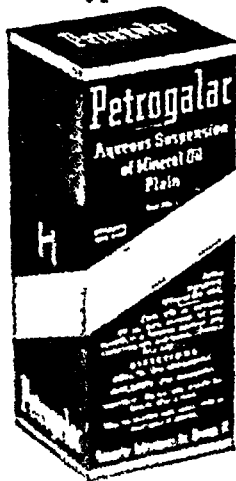
Please Mention this Journal when writing to Advertisers



For the Stay-at-Home

★★ **Petrogalar** *

*
Available at all
Pharmacies
in 5 Types



Shut in—No exercise—Appetite off—Sluggish bowel, all suggest the use of Petrogalar to assist Bowel Habit Time

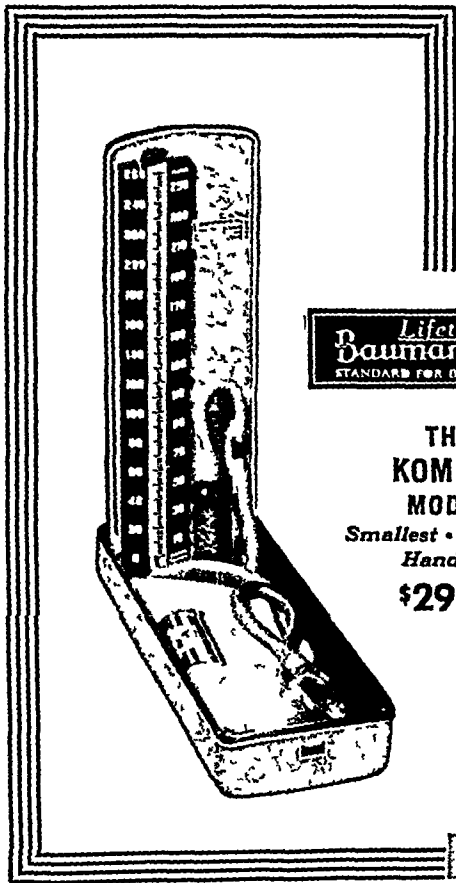
Petrogalar Plain adds unabsorbable fluid to the bowel content to encourage regular, comfortable elimination by purely mechanical means, free of habit-forming tendencies

Children and adults alike enjoy the delightful flavor of Petrogalar. It is easy to take, either from a spoon or in water, as desired.

**Trade Mark Petrogalar is an aqueous suspension of pure mineral oil each 100 cc of which contains pure mineral oil suspended in an aqueous jelly containing agar and acacia*

Petrogalar Laboratories, Inc • 8134 McCormick Boulevard • Chicago, Illinois

Please Mention this Journal when writing to Advertisers



Lifetime
Baumanometer
STANDARD FOR BLOODPRESSURE

**THE
KOMPAK
MODEL**

*Smallest • Lightest
Handiest*

\$2950

You serve with
when you serve with the

Precision

BAUMANOMETER

You'll be pleased with its handsome finish . . . its simplicity of operation . . . its compactness—yet the most important feature of the Lifetime Baumanometer cannot be seen . . . its scientific accuracy. This essential accuracy is built into every Baumanometer.

All Baumanometers are true mercury-gravity instruments . . . scientifically accurate, and guaranteed to remain so. Lifetime Baumanometers do not depend upon the elasticity of metal for their indications.

Your dealer can supply you.

*Get the **Facts** and you will buy a
Lifetime Baumanometer*

W. A. BAUM CO., Inc. NEW YORK
ORIGINATOR AND MAKER OF BLOODPRESSURE APPARATUS EXCLUSIVELY

For Hypo-Alkalinity

Kalak

TRADE MARK REG. U.S. PAT. OFF.

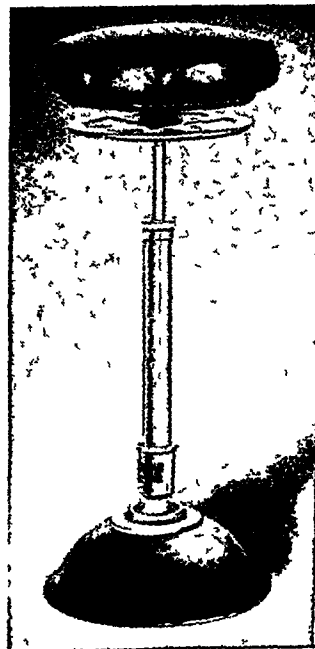
The All American
**ALKALINE
WATER**

SPARKLING!
NOT A LAXATIVE!

Complete literature on request

Kalak Water Co. of New York, Inc.

30 Rockefeller Plaza - New York, N. Y.



*Takes
the
Burden
Off Your
Feet*
•
*Ritter
Medical
Stool*
•

Tilts to any direction . . . adjustable height . . . soft, resilient seat . . . ends drudgery in the office . . . see it at your Ritter dealers or write direct. Ritter Equipment Company, Inc., Rochester, N. Y.



TABLETS THYROID SQUIBB

(Thyroid Glands Desiccated U S P XI)

Biologically Tested
to assure
dependable and
uniform activity

WHILE the treatment of hypothyroidism requires adequate dosage, many of the hazards to successful therapy may be eliminated by use of a standardized, dependable preparation of whole thyroid

Tablets Thyroid Squibb should find preference wherever a desiccated whole gland preparation is desired. They are made from carefully selected glands which are promptly desiccated to assure maximum activity. Pursuant to the requirements of the U.S.P. XI, the tablets are standardized for iodine content, 0.2 per cent iodine in thyroid combination. One part of the preparation corresponds to approximately five parts of the fresh gland.

In addition to meeting the above tests, each lot of Thyroid Squibb is physiologically tested as a further assurance of specific therapeutic activity. This biological assay is based upon the effect of the thyroid on the oxygen consumption of the guinea pig. Even though it is exactly and biologically standardized Thyroid Squibb costs no more.

Thyroid Squibb (Thyroid Glands Desiccated) is supplied in tablets, either uncoated or with enteric coating. Both forms are available in bottles of 100, 1000 and 5000 tablets in the following strengths: $\frac{1}{10}$, $\frac{1}{4}$, $\frac{1}{2}$ and 3 grains, also 5-gr tablets, enteric-coated only.

For literature write Professional Service Dept., 745 Fifth Ave.

E. R. SQUIBB & SONS, NEW YORK
MANUFACTURING CHEMISTS TO THE MEDICAL PROFESSION SINCE 1858

Please Mention this Journal when writing to Advertisers

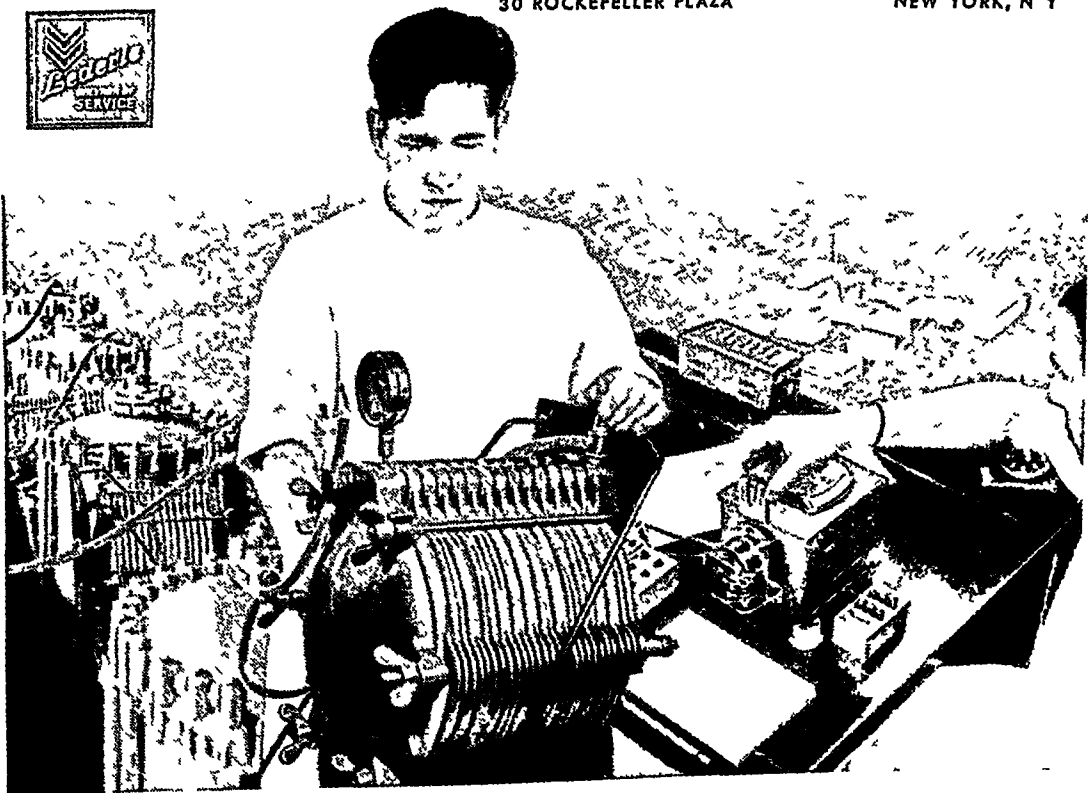
*A typical Lederle development—***SERUM REFINING**

SERUM SICKNESS used to be a serious obstacle to the successful application of serotherapy. So great was the fear of these reactions that at times the patient was even deprived of life saving treatment.

From 1906 to 1934 the "salting out" method of serum refining was virtually unchanged. It remained for Lederle's staff, long experienced in the problems of serum production, to establish firmly the value of a new process of serum refining. This process, based upon the phenomenon of peptic digestion, removes up to 90% of the troublesome proteins believed responsible for untoward serum reactions. Globulin Modified Antitoxins refined by this method may be expected to cause a minimum of reactions. They are higher in potency, smaller in volume and of greater clarity than previous antitoxins.

But serum refining is only one of many Lederle biological achievements. Antitoxins, serums, vaccines and toxoids from Lederle's 200-acre serum farm protect countless individuals from the ravages of disease all over the world.

LEDERLE LABORATORIES, INC
30 ROCKEFELLER PLAZA NEW YORK, N. Y.



Have YOU Read the Advertisements?

DON'T take advertising in the ANNALS for granted. Here assembled are the current announcements of a carefully selected list of reliable medical firms. The number of advertisements is limited; pharmaceutical products advertised must be accepted by the Council on Pharmacy and Chemistry, irrelevant ads are eliminated

Much effort is expended in obtaining these advertisements, the firms invest large sums for advertising

Support *your journal* by reading these advertisements and patronizing the advertisers!

BLACKOUT THE SHADOW!



CLOSE to all of us is the threatening spectre of tuberculosis. No respecter of persons, it lurks in every corner, may strike at any moment. *More people between 15 and 45 die from tuberculosis than from any other disease.*

Yet tuberculosis *can* be driven from the face of the earth. Since 1907 your Local Tuberculosis Association has helped reduce the toll of tuberculosis by 75%!

By buying Christmas Seals you will help us complete the job—and make this a safer world for yourself and your loved ones



Buy
**CHRISTMAS
SEALS**

MULL-SOY



MULL-SOY SOY BEAN MILK-SUBSTITUTE

The principal soybean protein is Glycine which is composed of the following AMINO ACIDS: Tyrosine - Cystine - Histidine - Glycine - Tryptophane - Arginine - Aspartic acid - Hydroxyglutamic acid and several others.



*Free Sample and Literature
Gladly Sent Upon Request*

THE MULLER LABORATORIES
3156 Frederick Ave
BALTIMORE MARYLAND

MULL-SOY



JOIN

AMERICAN RED CROSS

An Effective Medicinal Weapon Against Depressions

Mild pathological depressions may accompany a variety of clinical syndromes. In addition to prescribing whatever forms of therapy are indicated for the individual condition, it may also be advisable to treat the underlying or concomitant depression.

If, in the judgment of the physician, treatment of this depression appears advisable, the administration of Benzedrine Sulfate Tablets will often prove useful. In depressive psychopathic cases the patient should be institutionalized.

Benzedrine Sulfate Tablets offer "a therapeutic rationale which, in its very efficiency, cuts across the old categories" (Parker, M. M. — J. Abnorm. & Soc. Psych., 34:465, 1939).

Initial dosage should be small, 2.5 to 5 mg. If there is no effect this should be increased progressively. "Normal Dosage" is from 5 to 20 mg. daily, administered in one or two doses before noon.

Benzedrine Sulfate Tablets are now manufactured in two sizes. In writing prescriptions please be sure to specify the tablet-size desired, either 5 mg. or 10 mg.



Benzedrine Sulfate Tablets

Brand of amphetamine sulfate



SMITH, KLINE & FRENCH LABORATORIES, PHILADELPHIA, PA.

Please Mention this Journal when writing to Advertisers



and other known factors of the
VITAMIN B COMPLEX
including nicotinic acid

MEAD'S BREWERS YEAST TABLETS • Each Mead's Brewers Yeast Tablet contains 20 International units of vitamin B₁ (thiamin — the antineuritic factor) and 20 Sherman units of vitamin G (riboflavin). Clinical tests have shown the product to be rich also in nicotinic acid, for the prevention and treatment of pellagra. Supplied in 6-grain tablets in bottles of 250 and 1,000.

MEAD'S BREWERS YEAST POWDER • Each gram ($\frac{1}{2}$ teaspoon) supplies 50 International units of vitamin B₁ and 50 Sherman units of vitamin G (the same potency as Mead's Brewers Yeast Tablets), as well as nicotinic acid. Mixes readily with various vehicles the physician may specify in infant feeding. Supplied in 6-oz. bottles.

Mead's Brewers Yeast is nonviable and is vacuum-packed to prevent oxidation. Packed in brown bottles and sealed cartons for greater protection.

MEAD JOHNSON & COMPANY, EVANSVILLE, INDIANA, U. S. A.

Please Mention this Journal when writing to Advertisers

ANNALS OF INTERNAL MEDICINE

VOLUME 15

NOVEMBER, 1941

NUMBER 5

FAT METABOLISM IN DIABETES MELLITUS*

By WILLIAM C STADIE, M D , *Philadelphia, Pennsylvania*

THE enormous amount of research on the abnormal metabolic processes of diabetes mellitus since the time of v Mehring and Minkowski has failed to bring unity of conviction to students of the disease. We find today, as in earlier times, two opposing hypotheses still striving for supremacy. These two hypotheses may be briefly stated as follows:

I The under-utilization hypothesis states that the major defect in the intermediary metabolism of the diabetic is the inability of the tissues to oxidize sufficient carbohydrate for normal metabolic needs. In consequence, ingested carbohydrate and that derived from protein is excreted.

II The over-production hypothesis postulates that the diabetic has no essential impairment of carbohydrate utilization in the periphery provided compensatory hyperglycemia is maintained. The primary defect lies in the liver which in diabetes produces an excess of glucose from fatty acids as well as protein.

TABLE I

Current Theories of the Diabetic Defect

- | | | |
|----|-------------------|--|
| I | Under-utilization | The peripheral tissues, without insulin, cannot oxidize carbohydrate |
| II | Over-production | The liver, without insulin, converts an excess of fatty acids to glucose |

No matter which of these hypotheses is the true one, the complete diabetic animal is in a bad way. According to the under-utilization hypothesis, he is losing all of the energy derivable from carbohydrate, and about 50 to 60 per cent of that from protein. Hence, he is forced to fall back upon fat as the chief source of his energy requirements. According to the over-production hypothesis, the diabetic is pouring into the urine large amounts of fat in the form of sugar. In either case the question of fat metabolism becomes the paramount issue and it becomes imperative, therefore, to examine the hypo-

* Read at the Boston meeting of the American College of Physicians April 21, 1941
From the Department of Research Medicine, University of Pennsylvania

theses of fat metabolism which grew up simultaneously with the development of these two hypotheses concerning the metabolic defect

There is abundant evidence that a considerable fraction of the total fat metabolism is initiated in the liver. Differences of opinion arose as to the mechanisms of this hepatic fat oxidation and split the diabetic camp into two. The contending hypotheses are summarized in table 2. According to the

TABLE II

Contending Hypotheses Concerning the Preliminary Oxidation of Fatty Acids in the Liver

- II-A Fatty acids oxidized to ketone bodies + acetic acid
- II-B Fatty acids oxidized to ketone bodies + glucose
- II-C Fatty acids oxidized to ketone bodies only

first of these, fats are preliminarily oxidized in the liver to ketone bodies plus a two-carbon compound, i.e., acetic acid. In the normal subject these are completely oxidized in the periphery, but in the diabetic the oxidation of the ketones is blocked. This represents the position of the under-utilization hypothesis.

The second hypothesis states that the fats are initially converted by the liver to glucose as well as ketone bodies. Both are equally well oxidized in the periphery by both normals and diabetics. This represents the position of the overproduction hypothesis.

The third hypothesis states that fats are completely converted in the liver to ketone bodies only. These are freely utilized by the peripheral tissues of the diabetic. This position represents, indeed, a new departure and is the one for which experimental evidence will be given.

Several influences converged to throw the first of these hypotheses into the limelight and obscure the others. These were: First, the ascendancy of the under-utilization school led by Lusk; second, the strong position of the Knoop hypothesis of successive beta oxidation of fatty acids so strongly advocated by Dakin and Embden; and third, the development by Woodyatt and Shaffer of the hypothesis of the obligatory coupling of ketone oxidation with carbohydrate oxidation. It is necessary to examine these hypotheses closely since they are intimately concerned with the problem of the metabolic defect in diabetes.

TABLE III

Current Hypotheses of Fat Metabolism in the Diabetic

- I Knoop hypothesis of successive beta oxidation
Long carbon chains of fatty acids oxidized two carbons at a time with formation of acetic acid + one ketone molecule per molecule of fatty acid
E.g. Palmitic + 6.5 O₂ = 1 ketone + 6 acetic
- II Ketones oxidized only by obligatory coupling with carbohydrate oxidation
- III Fat converted to carbohydrate by liver

According to the successive beta oxidation hypothesis, the oxidation of the long naturally occurring even numbered fatty acid chains containing 16 or more carbon atoms would proceed as follows. Beta oxidation would split off from the fatty acid molecule, one acetic acid leaving a residual fatty acid

shorter by two carbons. This mode of oxidation would continue so that each fatty acid would be degraded through a succession of fatty acids each shorter by two carbons than its immediate precursor. Finally, there would result one molecule of acetoacetic acid or beta oxybutyric acid, i.e., the ketone bodies. For every molecule of fatty acid oxidized only one molecule of ketone would be formed. The residual ketones could be oxidized only by one mechanism, namely by the simultaneous oxidation of a definite amount of carbohydrate defined by the ketogenic-antiketogenic ratio. In the diabetic, since there was no carbohydrate oxidation, the ketones accumulate as toxic or useless by-products of fat oxidation which are excreted in toto.

This combination of hypotheses was eagerly accepted by the under-utilization school. For it made it possible to explain how the complete diabetic who, losing 70 to 80 per cent of the energy from protein and 100 per cent of that from carbohydrate, could still exist. There was the 50 per cent of the original energy of the fat in the form of acetic acid. Moreover, the formation of this easily oxidizable and readily diffusible substance avoided the necessity of postulating the formation of carbohydrate from fat. And finally, the discovery of the ketogenic-antiketogenic ratio afforded a ready explanation, which appeared quantitative, of the marked influence of carbohydrate upon urinary ketone excretion.

The position of the over-production school was less definite as to the chemical reactions occurring during the oxidation of fatty acids in the liver. Much evidence, however, was marshalled to show that glucose was an end product of this oxidation, but this evidence brought little conviction to the under-utilizationists. Indeed, Lusk, the chief exponent of the under-utilization school in this country, characterized the possibility of the conversion of fat to carbohydrate as a "figment of the imagination" which should be relegated to "the realm of scientific superstition." However, the critical experiment which would decide the issue one way or another still remained to be done.

SCHEMATIC OXIDATION OF PALMITIC ACID BY DIABETIC LIVER

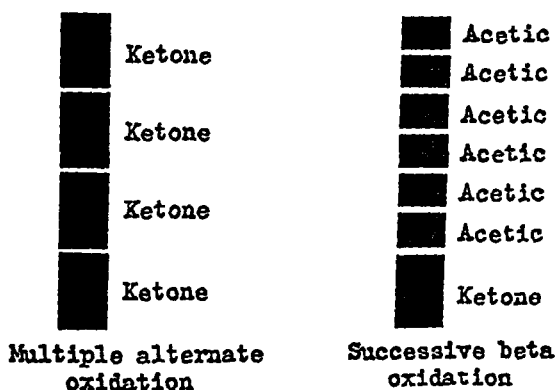


FIG 1

The English clinician Hurler in 1916 rejected the Knoop hypothesis mainly upon theoretical grounds and in its place proposed the multiple alternate oxidation hypothesis. This hypothesis, which has slowly accumulated evidence, is shown in a schematic way in figure 1 where it is contrasted with the Knoop hypothesis. The hypothesis postulates that there is a multiple oxidation at alternate carbon atoms along the entire length of the fatty acid chain. In consequence the entire fatty acid molecule is disrupted completely into ketone bodies only. In contrast, the Knoop hypothesis supposes a step by step splitting off of acetic acid molecules leaving a residue of one molecule of ketone. The chemical consequences of the multiple alternate oxidation hypothesis for the oxidation of a typical acid such as palmitic are as follows: (1) For the production of one molecule of ketone there should be required by the liver $1\frac{1}{4}$ molecule of oxygen instead of $6\frac{1}{2}$, (2) for every molecule of fatty acid oxidized there should appear four molecules of ketones instead of one, and finally (3) the oxidation of one molecule of fatty acid should yield no acetic acid whatever instead of six molecules.

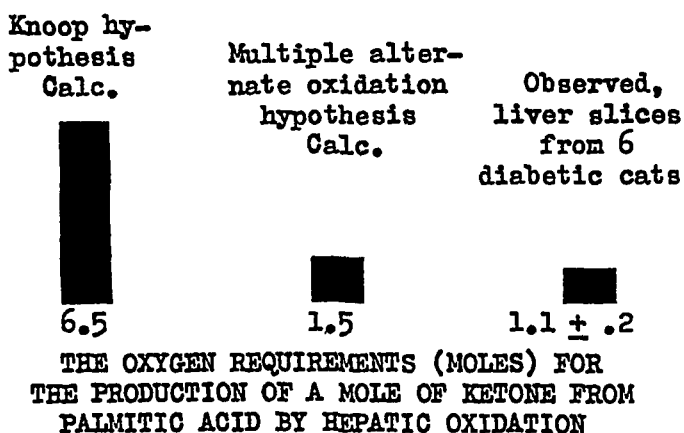


FIG 2

Now if a depancreatized cat with full blown ketosis is taken, the answer to this problem should be found in the fat metabolism of the liver. In association with Dr Francis D W Lukens, Director of the Cox Institute, and Dr John A Zapp, Jr, of the Department of Research Medicine, experiments were done, part of which are reported here. In general the method was as follows: two or three days after removal of the pancreas, the animal was sacrificed and liver slices were prepared and equilibrated in vitro in suitable buffers together with oxygen. Using appropriate analytical methods certain metabolic processes occurring in the liver could be followed.

In the first type of experiment shown in the slide we determined the moles of oxygen required by the liver to form one molecule of ketone. The Knoop hypothesis requires 6.5; the multiple alternate oxidation hypothesis requires 1.5. We found a mean value in six diabetic cats of 1.1. This ratio is not significantly different from that demanded by the multiple alter-

nate oxidation hypothesis but quite significantly different from that of the Knoop hypothesis

NON-FORMATION OF ACETIC ACID
BY LIVER SLICES FROM DIABETIC CAT (No. 106B)

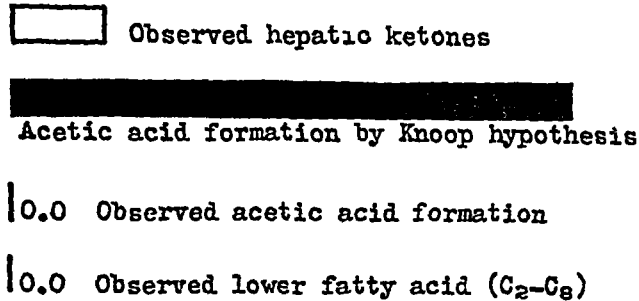


FIG 3

In the second type of experiment we looked for the possible formation of acetic acid in the slice from livers of diabetic cats. These livers were oxidizing fatty acids in a lively fashion as shown by abundant ketone formation. According to the Knoop hypothesis the large amounts shown on the slide should have been found, yet we found no acetic acid formation whatever. We also looked for the lower fatty acids containing one to eight carbons supposedly formed by successive beta oxidation but could find none.

THE BALANCE BETWEEN FATTY ACIDS OXIDIZED
AND KETONES FORMED BY LIVER
(Diabetic cats; phlorhizinized cats or rats)

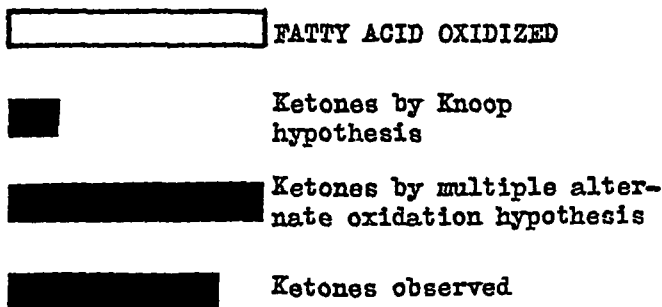


FIG 4

In the third type of experiment we measured the fatty acid balance of liver slices from diabetic cats. The Knoop hypothesis says that one fourth of the fatty acid oxidized should appear as ketones, the multiple alternate oxidation hypothesis says that all of the fatty acid oxidized should be converted into ketones. We found by experiment with eight diabetic or phlorizinized cats or rats that ketone formation practically accounted for all of the

fatty acid oxidized, a result anticipated from the multiple alternate oxidation hypothesis

The summation of the evidence in these experiments brought us to the conviction that the Knoop hypothesis of successive beta oxidation as an explanation for the major part of the fatty acid oxidation occurring in the liver must be abandoned and replaced by the multiple alternate oxidation hypothesis

THE OXIDATIVE METABOLISM OF
LIVER SLICES FROM SIX DIA-
BETIC CATS.

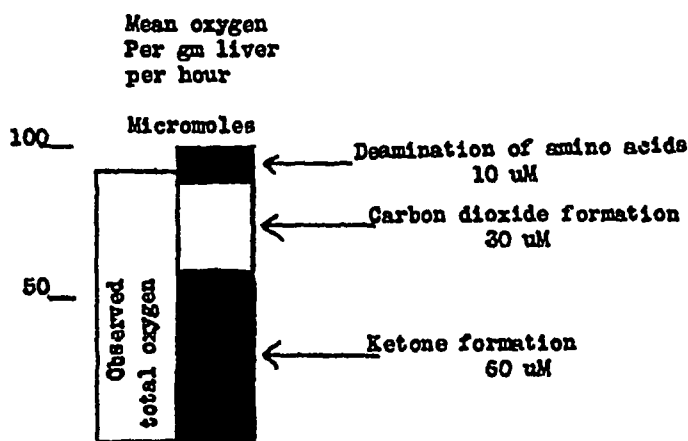


FIG 5

Published by permission from the Trans Assoc Am Phys

A moment's reflection should show that these experiments enable us to write the reaction for the oxidation of fatty acids by the liver of the diabetic cats. We find that it is not necessary to include glucose in that reaction. However, two other types of evidence were obtained on this point. Firstly, an oxidative balance of the liver slices from diabetic cats can be obtained. Three known oxidative processes were independently measured and the oxygen required for each calculated. They are shown in figure 5 and are (1) formation of urea by deamination of amino acids, (2) formation of carbon dioxide, and (3) formation of ketone bodies. The sum of these three was found, in the case of six diabetic cats, to be not significantly different from the total observed oxygen uptake. In other words, there was no oxygen available for any other oxidative process. But the conversion of fats to glucose requires oxygen, and these same cats excreted one to four hours before the experiment amounts of glucose which if it came from fats would have required all or more oxygen utilization than that actually observed. The experiment, however, shows that there was, in the metabolism of the liver, no oxygen whatever available for this synthesis; hence, we are again forced to exclude the possibility of glucose formation from fats in the liver of the diabetic cat.

In the second type of experiment bearing on this point, we constructed a balance sheet of the actual new formation of carbohydrates by the diabetic liver slice. Our data allowed us to calculate amounts of glucose which might arise from protein, lactic acid, or glycerol. Within the limits of error we found no unaccounted for new carbohydrate which could be attributed to fat. In contrast to our inability to demonstrate formation of glucose from fat was our experience with a known precursor of carbohydrate. For example, these same liver preparations in the presence of lactic acid formed new carbohydrate up to 10 mg per gm per two hours, an amount sufficient to account for a large fraction of the glucose (75 per cent) actually excreted by the cat in a preliminary period of observation.

These experiments on depancreatized cats reinforced by new and old evidence in the literature both in experimental diabetes and diabetes mellitus, have brought us the conviction that the hypothesis which maintains that there is conversion of fatty acids to glucose in the liver is untenable.

Apparently then, the complete diabetic is producing nothing but ketones by oxidation of fats in the liver, and he would certainly be in a sad state if he could not utilize these ketones peripherally, for then fats would be gone, carbohydrates gone, and protein almost gone, and he would have nothing to fall back upon for his energy requirements. The demonstration that the diabetic could utilize ketones peripherally became of prime importance. In five ways (two are presented here) we showed that the diabetic does, in fact, utilize them.

METHOD I. KETONE UTILIZATION BY 8 DEPANCREATIZED CATS.

KETONES FORMED BY LIVER SLICES

Per Kg body weight per hour

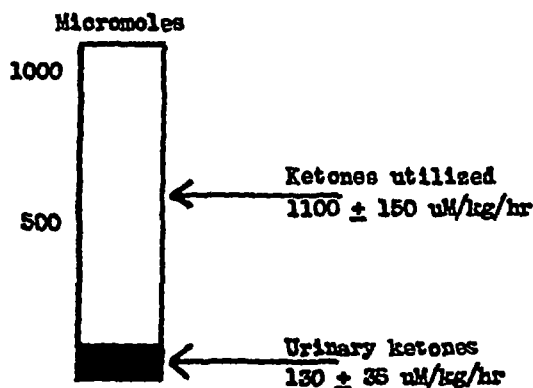


FIG 6

First we measured the urinary ketone excretion in the diabetic cat. Then the animal was sacrificed and ketogenesis by the liver slices measured. In all cases the total ketone formation by the liver was greatly in excess of the urinary ketone excretion. The difference can only represent the ketone body utilization by the peripheral tissues, chiefly muscle, of the intact diabetic cat. The value found is equivalent to 1.9 gm of fat/kg/day.

Method II. 'SYNTHETIC' DIABETIC CAT.

KETONE UTILIZATION

Per Kg cat per hour
Micromoles

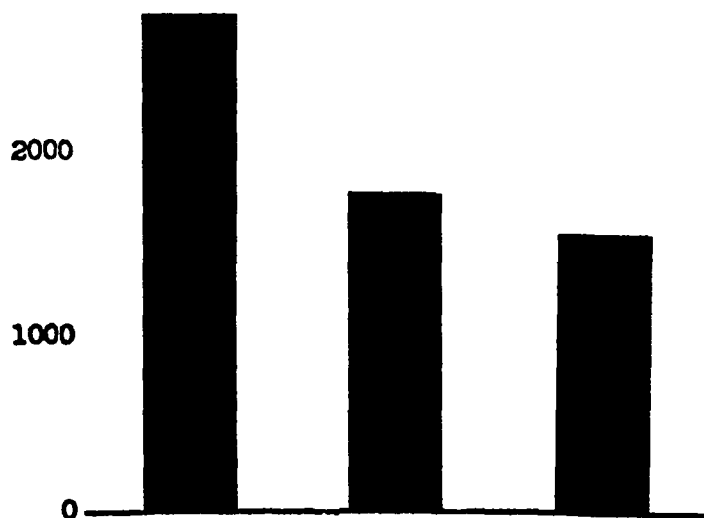


FIG 7

Published by permission from the Trans Assoc Am Phys

In the second method we again showed that the muscle tissue from diabetic cats utilized ketone bodies. In this case the diabetic muscle tissue was equilibrated together with a slice of the liver from the same cat. By this device the muscle tissue was continuously supplied with ketone bodies formed by the diabetic liver and the conditions in the living cat simulated. By the use of appropriate controls it was possible to calculate the ketone utilization which was found to be, in terms of fat, equal to 3.7 gm/kg/day.

In the third method, we showed more directly that the muscle tissue of the diabetic animal utilized ketones. Muscle tissue was equilibrated with known amounts of acetoacetic acid. In all cases the ketone was diminished after equilibration with the muscle, and the calculated rate of utilization was equivalent to 1.6 mg of fat/kg./day.

These results obtained by the use of surviving tissue equilibrated in vitro were corroborated in the intact diabetic cat by the determination of the ketone difference between the portal and the hepatic blood. The outgoing

hepatic concentration was always found to be higher than the ingoing portal concentration. Calculations using estimated hepatic blood flows showed that hepatic ketogenesis was greatly in excess of urinary ketone excretion. In other words there was, as with the slices, considerable ketone utilization by the peripheral tissues of the diabetic cat, which in the mean was found to be equivalent to 2.3 gm of fat/kg/day.

TABLE IV
Ketone Utilization by Depancreatized Cats

Method No	Number of cats	Ketone utilization, per Kg cat per hour
		Micromoles
I Ketone formation by liver slices minus ketone excretion	8	1100±150
II "Synthetic" cat	3	2070±265
III Acetoacetic acid equilibrated with muscle	5	915±265
IV From portal vein-hepatic vein ketone conc and blood flow	3	1265±260
Mean	19	1340±260

All these results are in accord with one another and with other data in the literature. The situation seems now to be fairly clear. It appears highly reasonable to exclude the over-production hypothesis as an explanation of the diabetic defect and adhere to the under-utilization hypothesis. The diabetic in calling for reserve energy from fat can muster a considerable fraction of his needs by oxidizing fatty acids to ketones in the liver. These ketones are freely used in the periphery without insulin and without the necessity of simultaneous coupling with the oxidation of carbohydrates.

But there still remained in the ketogenic-antiketogenic ratio a remnant of the obligatory coupling hypothesis, that is, the hypothesis epitomized by the aphorism "the fats burn in the flame of the carbohydrates." This ratio has been established in human cases of diabetes and it became necessary to reexamine the assumptions and calculations upon which it had been based.

The assumptions were clearly stated by Shaffer, and I quote "The hypothesis states that antiketogenesis in the human subject is based upon a ketolytic reaction in the body between acetoacetic acid, the first formed of the acetone bodies, and a derivative of glucose (or other antiketogenic substances), the compound being further oxidized, but that failing to react with ketolytic substance, acetoacetic acid is resistant to oxidation, accumulates, and is excreted. The fact that one finds at the threshold of ketosis an approximately constant ratio between the number of molecules of the precursors of acetoacetic acid and of glucose in the metabolic mixture, must mean that further oxidation of acetoacetic acid constantly taking place under normal conditions is accomplished through a chemical reaction with a derivative of glucose."

Fortunately, there are in the literature a series of classical cases reported before the advent of insulin when severe ketosis was of necessity a frequent accompaniment of the disease. The data include calorimetric measurements of the metabolic mixture of protein, fats, and carbohydrates together with total ketone excretion. Hence it is possible to calculate the total carbohydrate or so-called antiketones oxidized, the total fat catabolized, and the total fat utilized. The best way to examine the data is to put the hypothesis in the form of an equation. Curiously enough this never was done. Figure 8 shows the data in the case of Bessie B. reported by Wilder, Boothby and

**Diabetes Mellitus, Bessie B.
(Wilder, Boothby, and Beeler, 1922)**

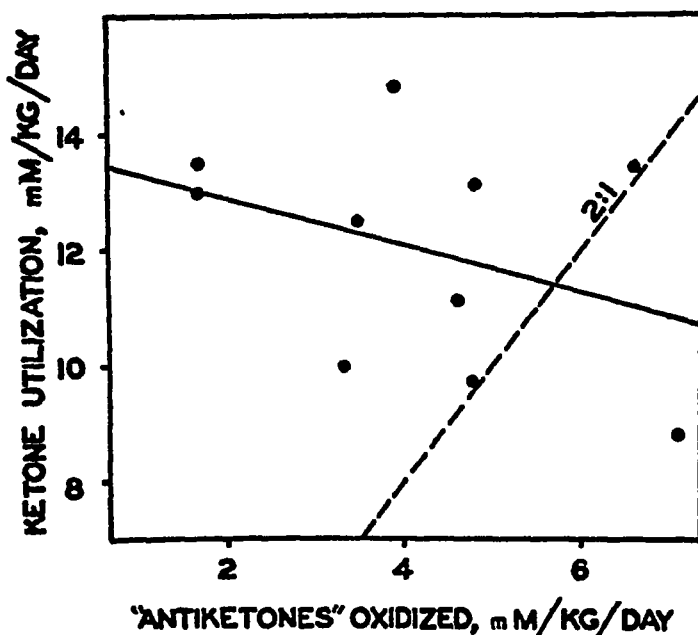


FIG 8

Published by permission from the Jr Clin Invest.

Beeler. The ordinate shows the fat utilization expressed in terms of mM of ketones. The abscissa shows the mM of antiketones oxidized. The hypothesis is expressed by the dashed line for a ketone-antiketone ratio of 2:1. But the true line calculated from the data runs in the opposite direction with no relation whatever to the theory. Moreover, it is important to note that the intercept constant when antiketones oxidized were zero is about 14 mM, equivalent to about 1 gm of fat/kg/day. This value is greatly different from zero which it should be according to the theory. That is to say, Bessie B. was utilizing ketones even in the practically complete absence of carbohydrate oxidation, a conclusion in conformity with our experiments with diabetic cats and opposed to the obligatory coupling hypothesis.

One more representative case is shown, that of Cyril K., reported by Gephart, Aub, DuBois and Lusk. Of all the cases in this group the dotted

line for the theory shows the best agreement to the "eye" But this agreement is entirely specious when the statistical analysis is considered, for the true line shows a slope of 7 instead of 2 and moreover when antiketones are zero, that is when no carbohydrate whatever was being oxidized, Cyril K was completely oxidizing 90 gm of fat per day without ketonuria and without simultaneous oxidation of carbohydrate, a conclusion in conformity with our experiments on diabetic cats

Diabetes Mellitus, Cyril K.
(Gephart, Aub, Du Boid, and Lusk, 1917)

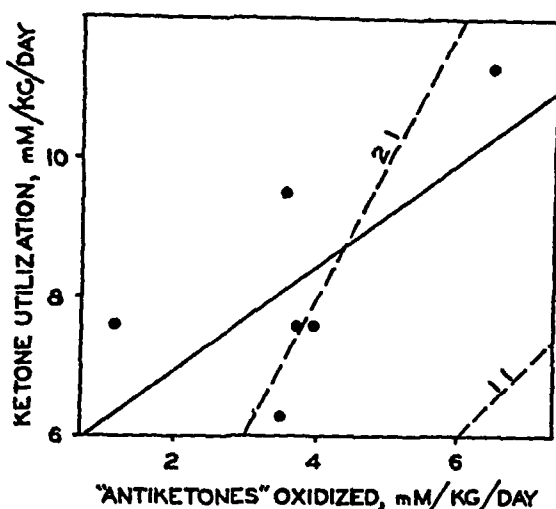


FIG 9

Published by permission from the Jr Clin Invest

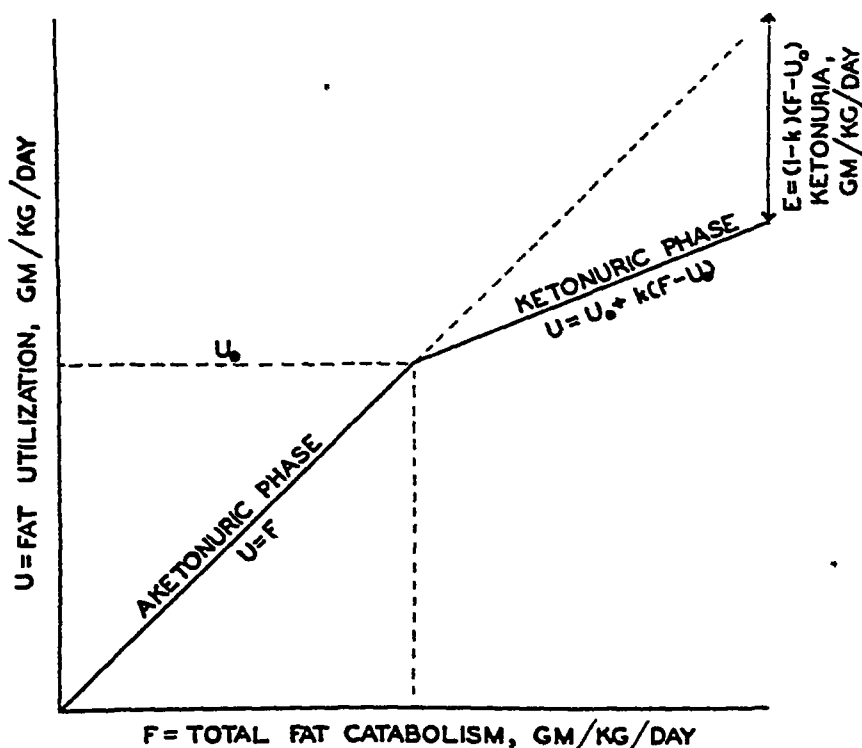
Four other cases for which data were available showed the same as did these two illustrative cases, and it seemed to us that the last remnant of the obligatory coupling hypothesis as expressed in the ketogenic-antiketogenic ratio had vanished. It remained, therefore, to formulate an hypothesis of fat metabolism in diabetes mellitus which would be in conformity with these observations. The following appears to fulfill these requirements.

Up to a certain level all fat catabolized is completely utilized, hence, there is no ketonuria. Beyond this level all fat catabolized is not completely utilized, hence, part of the fat catabolized is excreted in the form of ketone bodies.

The relation of carbohydrate to fat metabolism is a simple inverse one. The greater the carbohydrate utilized, the less is the fat metabolism, that is, carbohydrates spare fats.

The diagram in figure 10 shows the implications of this hypothesis. The abscissa shows F , the total gm/kg/day of fat catabolized, that is, fat poured into the stream of intermediary metabolism. The ordinate shows U , the total fat utilized, that is the amount of fat which is completely oxidized.

There are two phases in the metabolism of fat. The first is the aketonuric phase, the second is the ketonuric phase. Starting at zero and increasing the amount of fat catabolized, we pass through the aketonuric phase along the line marked $U = F$. Here all fat in the metabolic stream is completely utilized and there is no ketonuria. But at any given state of activity, the ability of the diabetic to mobilize exactly that amount of fat which can be completely utilized appears to be limited. This upper limit I call the maximal aketonuric fat utilization indicated by U_0 , the horizontal line on the



SCHEMATIC REPRESENTATION OF FAT METABOLISM IN DIABETES MELLITUS

FIG 10

Published by permission from the Jr Clin Invest

diagram. If the call for fat calories exceeds this aketonuric level, it is answered in the following way. Extra fat is catabolized above and beyond this level, but only a part of this extra fat is completely utilized. This is shown by the bending of the line marked "ketonuric phase" away from the extended dotted line which would represent complete utilization. The difference in fat between these two lines, indicated by the double arrow on the right, is not utilized, and hence is excreted in the form of the ketones. In other words, the diabetic can only increase his energy from fat above the basal aketonuric level by paying for it with base combined with urinary ketone acids, at the risk of acidosis.

This hypothesis can easily be tested by applying the data of diabetic cases in the ketonuric phase. The first illustrative case is No 740 of Joslin. The data represent, as before, the metabolic mixture determined by calorimetric

methods In the diagram on the left the abscissa shows the total fat catabolized expressed in micromoles of ketones per kg per hour The ordinate shows the total fat completely utilized The observations for a series of days in this case fall about the straight line as expected from the hypothesis At 1200 catabolism and utilization are equal, hence there was no ketonuria, 1200 micromoles, equivalent to 2 gm of fat/kg /day, was the aketonuric fat utilization in this case When this level was exceeded, for example at 1800 micromoles, only 1600 were utilized In other words about $\frac{1}{3}$ of the total fat catabolized was excreted as ketone bodies The diagram on the right of figure 11 shows the same data plotted according to the ketogenic-antr-

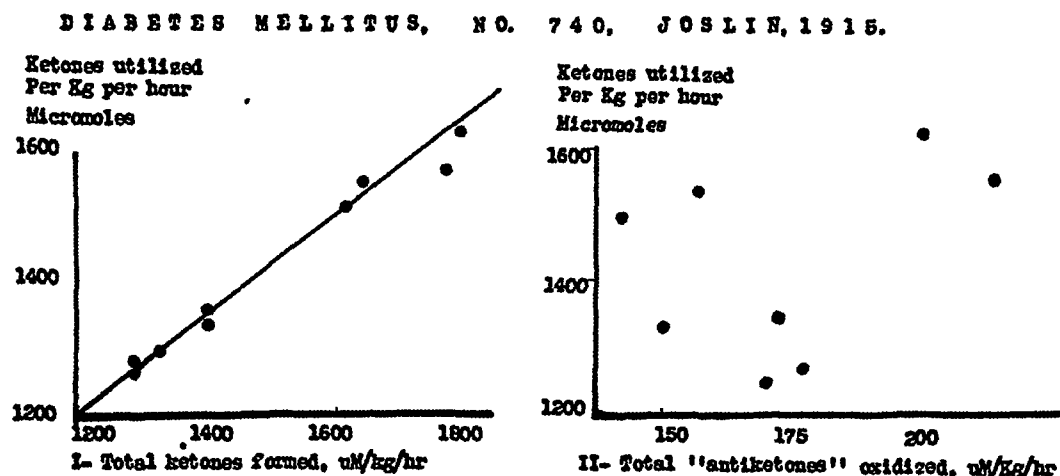


FIG 11

Published by permission from the Trans Assoc Am Phys

ketogenic hypothesis It is obvious, as was shown before, that there is no relation between ketone utilization and the oxidation of the so-called anti-ketones

By way of illustrating the fact that the hypothesis could just as well have been framed in terms of urinary ketone excretion I show the data in one case, that of Cyril K The total fat mobilized is shown along the abscissa, and the urinary ketones are shown on the ordinate in the same units The data fall about a straight line as expected Note that when the urinary ketones are zero, fat utilization is 1500 $\mu\text{M/kg/hr}$ equivalent to 150 gm of fat per day This was Cyril K's basal aketonuric fat utilization value Note further that when he increased his fat catabolism by 1000 μM he excreted about 600 out of this extra 1000 In other words, Cyril K could use only about 40 per cent of the fat he catabolized above his basal aketonuric level

All the cases for which there were data available in the literature showed the same relations as those shown The analysis of these cases is shown in table 5 There are 12 cases altogether, all from different clinics but studied by essentially the same methods In the third column is shown the basal aketonuric fat utilization value With the exception of Mosenthal and

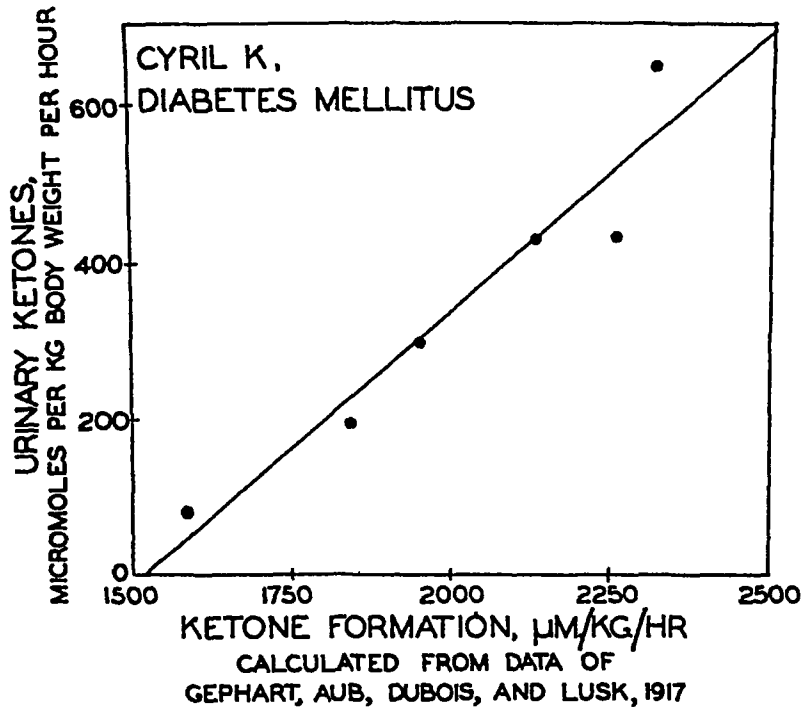


FIG 12

Published by permission from the Trans Assoc Am Phys

Lewis' case, the one case with infection and fever, the values for the aketonuric fat utilization value are all concordant. The mean value is equivalent to 2.5 gm of fat/kg/day.

We take these results, which are in agreement with our experiments with diabetic cats, to constitute evidence supporting the hypothesis of fat metabolism in the diabetic here advanced.

TABLE V

Summary of Maximal Basal Aketonuric Fat Utilization in Cases of Diabetes Mellitus

Case	Reference	Maximal aketonuric fat utilization in equivalents of ketone bodies	Coefficient of excess fat utilization
<i>Group I</i>		<i>mM per kg per day</i>	
Cyril K.	Gephart, Aub, DuBois and Lusk (25)	35	+0.41
Bessie B.	Wilder, Boothby and Beeler (24)	34	+0.75
Kramer	Shaffer (22)	35	+0.28
740	Joslin (23)	28	+0.75
E. W.	Mosenthal and Lewis (27)	(47)*	-0.38
Jervis B.	Richardson and Ladd (26)	23	+0.84
<i>Group II</i>			
Ray II	Richardson and Ladd (26)	37	
Chris Q.	Richardson and Ladd (26)	26	
Harold J.	Richardson and Ladd (26)	37	
George H.	Richardson and Ladd (26)	37	
Frank B.	Richardson and Ladd (26)	37	
K. A.	McClelland, Spencer, and Falk (28)	40	
Mean (11 cases) Equivalent in grams of fat		34 ± 1.6 (S.E. of mean) 2.5 ± 0.12	

* Excluded from basal mean on account of fever (102° F.).

The results of these experiments, together with related evidence in the literature, may be summed up as follows

1 The diabetic who by reason of insulin lack is unable to utilize carbohydrates to the full measure of his metabolic needs, must fall back on fat for his energy requirements. Part of this need is met by the initiation and completion of fat oxidation in the muscles themselves. However, a considerable fraction estimated as $\frac{1}{3}$ to $\frac{1}{2}$ of the total caloric needs from fat is obtained by a preliminary oxidation of fats in the liver to ketone bodies only. Neither acetic acid nor glucose is formed by this oxidation. These hepatic ketone bodies are freely utilized for energy by the periphery without insulin and without the necessity of simultaneous carbohydrate oxidation. This reserve mechanism, however, appears to be incapable of fine regulation so that when the demand for fat calories exceeds a certain level, approximately 25 gm of fat/kg /day for the resting state, ketone bodies in excess of needs are formed by the liver. The excess is excreted as ketones in the urine. If this excessive fat catabolism continues unchecked, ketosis and coma follow.

STUDIES OF THE FACTORS CONCERNED IN EDEMA FORMATION. II. THE HYDROSTATIC PRESSURE IN THE CAPILLARIES DURING EDEMA FORMATION IN RIGHT HEART FAILURE*

By GEORGE FAHR, M D , and IRVING ERSHLER, M D ,
Binghamton, New York

ONE often hears eminent clinicians state that cardiac edema is due to increased permeability of the walls of the capillaries consequent to oxygen deficiency or to stasis within these vessels. This, despite the fact that not infrequently the oxygen content of the venous blood from the edematous limb shows no very marked reduction, and marked reduction in oxygen content of the venous blood as in the cyanotic group of congenital heart disease, may not be associated with edema throughout a period of many years. Even more marked degrees of oxygen reduction are far from the anoxemia levels at which capillary permeability shows a qualitative change. The degree of anoxemia that Landis¹ has shown to be necessary to produce a conspicuous change in the permeability of the wall of the capillaries of the frog mesentery is probably never found in heart failure except just before death. Moreover, our investigations of the edema fluid obtained from the legs in right heart failure lend no support to the idea of increased capillary permeability. This fluid contains the salts of the plasma in almost the same concentration as in the plasma itself, the slight difference being explained by the so-called Gibbs-Donnan equilibrium. The protein content of cardiac edema fluid varies from 0.1 to 0.5 per cent which is nearly the same as the content of edema fluid in nephritis and nephrosis[†]. This moderate amount of protein content in the edema fluid which corresponds to colloid osmotic pressures of from 0.25 to 1.5 mm Hg is such that it alone could not possibly explain edema formation.

Let us see what light can be shed on the problem of edema formation in right heart failure by a review of our knowledge of fluid exchange between the blood plasma in the capillaries and the surrounding tissue spaces. All physiologists now agree with Starling² that the capillary is the site of fluid exchange between the blood plasma and the tissue spaces and that the capillary wall is a fairly perfect ultrafilter in most parts of the body, certainly in the subcutaneous areas where most of the edema accumulates. This ultrafilter allows water and salts to pass freely across it but prevents the passage of the plasma proteins. These capillary ultrafilter membranes are not completely

* Received for publication October 28, 1940

† From the Department of Medicine, University of Minnesota and Minneapolis General Hospital

‡ These data will be published in the near future in a paper by Fahr and Koschnitzke

perfect but in certain areas of the wall they allow plasma proteins to pass through them so that the edema fluid, when carefully collected and analyzed, usually shows a small protein content, in our investigations between 0.1 and 0.5 per cent.

In 1896 Starling³ performed experiments in edema and lymph formation on dogs. On the basis of his experiments, he discussed the factors involved in edema and lymph formation. The conclusions of Starling painstakingly developed by Schade⁴ will for a long time to come form the basis for well founded theories of edema formation in nephritis and in heart failure. According to the Starling-Schade concept there must be a balance between the "effective" hydrostatic pressure in the capillaries and the "effective" osmotic pressure of the plasma proteins. If the "effective" hydrostatic pressure throughout the capillaries is greater than the "effective" colloid osmotic pressure of the blood plasma, there must be a continuous filtration of the blood plasma minus the proteins across the capillary wall into the surrounding tissue spaces. If the lymph flow is unable to remove this filtrate as rapidly as formed, it must accumulate in the tissue spaces and edema must result. The "effective" colloid osmotic pressure is the osmotic pressure of the plasma proteins plus the diffusible ion pressure difference (Donnan effect). It is this "effective" colloid osmotic pressure which we measure in our osmometer⁵. The "effective" hydrostatic pressure is the actual blood pressure within the capillaries minus the pressure of the extracapillary tissue fluid. As a rule, this tissue pressure outside the capillaries, at least in the subcutaneous spaces, and with the body in supine position, is small and probably negligible until edema accumulates when it may be necessary to measure it and subtract it from the actual intracapillary pressure in order to arrive at the "effective" filtering pressure. Whenever tissue fluid or edema fluid begins to accumulate beyond the normal amount the lymph flow increases. When the rate of formation of edema fluid reaches a certain velocity, lymph flow can not keep up with the filtration rate, and more and more edema fluid accumulates and finally becomes clinically demonstrable. When about two quarts of edema fluid accumulate in a leg, it is possible to demonstrate pitting edema.

Figure 1 is a schema which illustrates the elementary process of fluid exchange in the capillaries in what may be called the "basal" state, i.e., when the body is placed in the supine position and the capillaries are all at approximately the right auricular level. According to Landis⁶ measurements, which measurements have been confirmed by us, the average blood pressure at the arterial end of the capillary is 32 mm Hg and the average blood pressure at the venous end of the capillary is 12 mm Hg. If it were not for the presence of the plasma proteins there would be a continuous filtration of water and salts from the plasma into the surrounding tissue spaces throughout the entire length of the capillary. The plasma protein particles, serum albumin and globulin, can not pass the ultrafilter membrane of the

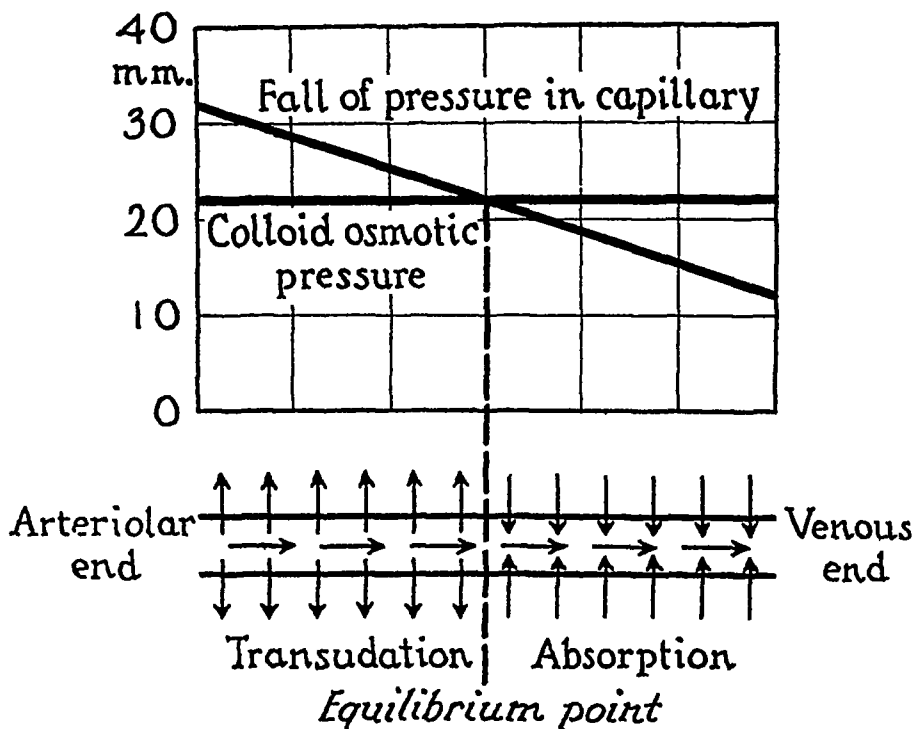


FIG 1 Graphic representation of fluid exchange in the capillaries of a normal person in supine position. In this position all the capillaries are very nearly at right auricular level.

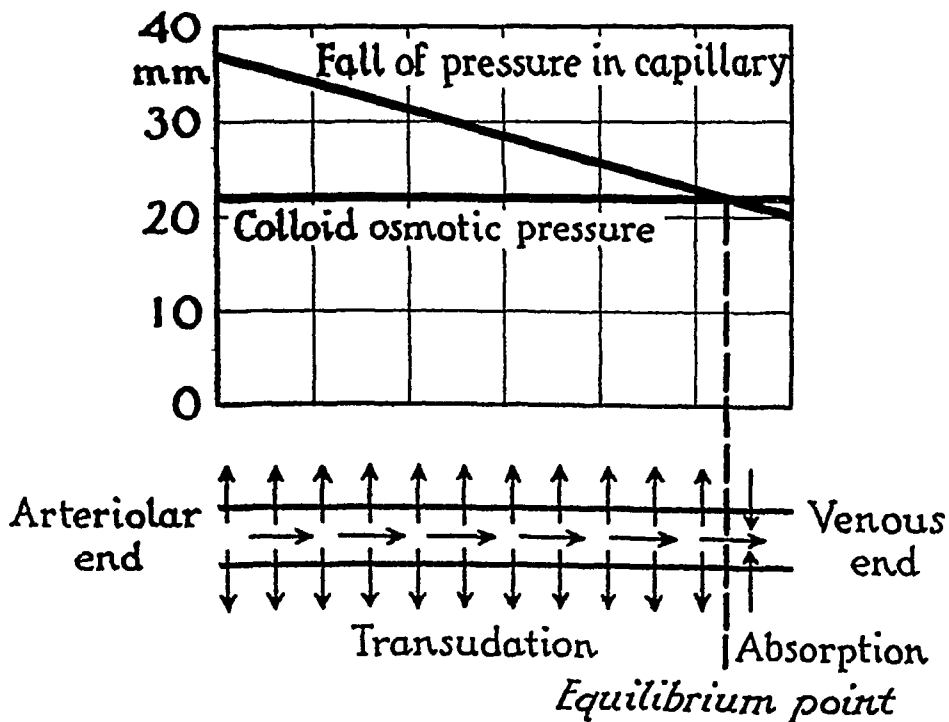


FIG 2 Graphic representation of fluid exchange in the capillaries of a case of right heart failure in which the capillary pressure at the venous end of the capillary is 20 mm Hg when the patient is in supine position. With this pressure at the venous end of the capillary, edema will develop when the patient is up and about and on no salt and water restriction.

capillary, they remain behind within the plasma and exert a force tending to resist the filtration of water and salts. The colloid osmotic pressure measures this force exactly. The average colloid osmotic pressure in human plasma is 22 mm Hg.⁷ Where the hydrostatic pressure within the capillary is greater than 22 mm Hg, water and salts will be filtered out of the blood plasma into the surrounding tissue spaces. Where the colloid osmotic pressure is greater than the hydrostatic pressure within the capillary, water and salt will be transported back from the tissue spaces across the capillary membrane into the plasma. Therefore, in the arterial end of the capillary filtration will take place continuously along the wall of the capillary until a point is reached where the hydrostatic pressure has fallen to the colloid osmotic pressure. From this point onward the capillary pressure decreases continuously and, the colloid osmotic pressure being greater than the hydrostatic pressure, water and salts are brought back into the capillaries. In a state of perfect equilibrium such as is represented in figure 1, which must be looked upon as an ideal case, there is just as much water filtered out of the arterial end of the capillary as is reabsorbed in the venous end. By increasing the capillary pressures at the arterial and venous ends, we can increase filtration above reabsorption. By reducing capillary pressures we can increase reabsorption above filtration. In the one case we get a tendency to edema formation unless the lymphatics can take care of the excess fluid filtered out of the capillaries. In the other case we would get a dehydration of the tissues with a subsequent hydrema of the blood plasma.

Numerous investigators⁸ studying dropsy formation in nephrosis and nephritis have proved that edema will tend to form when the colloid osmotic pressure is lowered from its normal value of about 22 mm Hg to a value of about 15 mm Hg, unless the intake of salt and water is reduced and the patient put to bed. It would, therefore, seem very probable that if the hydrostatic pressure in the capillaries would rise 7 mm Hg we would have exactly the same situation in regard to filtration and edema formation as we have in nephrosis and nephritis when the colloid osmotic pressure is reduced 7 mm Hg. Every clinician who measures venous pressures in right heart failure knows that edema tends to form when the venous pressure reaches about 170 mm H₂O, a rise of 100–110 mm H₂O or approximately 7–8 mm Hg above the normal. Therefore, it seems very probable that our hypothesis is correct, that a rise of intracapillary pressure of 7–8 mm Hg will be followed by edema formation.

In order to test out this hypothesis it is, of course, necessary to measure accurately the hydrostatic pressure within the capillaries during the formation of edema as well as during the period when edema is absorbing and diuresis is taking place. In order to measure the hydrostatic pressure within the capillary accurately, it is necessary to make direct measurements of this pressure by means of a very small cannula inserted into the capillary. Indirect methods of measuring capillary pressure are wholly unreliable and

give such varying results in the hands of various investigators that they can not possibly be used to solve our problem. Strax and DeGraff⁹ have collected the indirect measurements of capillary pressure made by the various investigators. These vary over a range of from 15 to 71 mm Hg. The lower values are such that the tissues would unquestionably soon become completely dehydrated and the higher values would necessarily lead to marked edema formation in normal persons.

In 1926 Landis¹⁰ succeeded in cannulating human capillaries with a very fine micropipette and was able to measure directly by means of a water manometer the actual hydrostatic pressure at the arterial end of the capillary, at the venous end of the capillary, and at the top of the capillary loop, i.e., approximately half way between the arteriolar and the venous end of the human capillary. He made over 100 determinations of intracapillary pressure. The mean pressure at the arteriolar end was 32 mm, at the height of the loop it was 18 mm, and at the venous end it was 12 mm Hg.

We have applied Landis' method in our problem of determining the capillary pressure during edema formation and after edema had disappeared in cardiac cases.* The micropipettes are drawn out to a diameter of 8–12 microns from fine glass tubing heated in a flame. They are then clamped in a micromanipulator which allows accurately controlled but very minute movements in the three planes of space. The micropipette is connected by flexible metal tubing to a manometer system. The height of the manometric column is changed by movement of the plunger of a syringe, controlled by a thumb screw. In this way pressure within the pipette is changed (When equilibrium is established blood corpuscles, which rush into the tip of the pipette when the capillary is pierced, oscillate to and fro with the heart beat. The point of exact pressure equilibrium, which is attained when the corpuscles oscillate about the same point for 5 to 10 seconds without continuous movement either into or out of the pipette, is quite distinct.) The entire system to the tip of the pipette is filled with physiological salt solution to which 0.3 per cent sodium citrate has been added. After the system has been properly filled and is free of air bubbles, the micropipette is driven through the epidermis of a finger a short distance behind the nail. The subjects are placed comfortably in the supine position with the finger at the level of the right auricle. This finger rests snugly in a plasticine mold. The capillary to be pierced, as well as the movements of the micropipette, and the movements of blood from the capillary in and out of the pipette are observed with a Spencer binocular dissecting microscope with a magnification of 85 times. The finger is illuminated with a Spencer universal microscope lamp No. 368.

The normal subjects and the patients are kept comfortably warm and the measurements are made at room temperature on naturally warm fingers. All

* We wish here to acknowledge our obligation to Dr. Landis for his advice in applying his method and for showing one of us (I.E.) how to overcome some of its difficulties.

the necessary precautions for making accurate measurements are taken. The introduction of the micropipette obliquely into the venous end of the capillary does not block flow in most cases and, therefore, the pressure reading on the manometer indicates the side-arm pressure at this point. One does not pierce the extreme venous tip of the capillary, and for this reason we may suspect that the capillary hydrostatic pressure at the extreme venous end of the capillary may be a little lower than the measured pressure. This difference is certainly no greater than 1 mm Hg. Occasionally some blocking of flow may take place during capillary pressure measurements at the venous end with an occasional measurement higher than the actual pressure within the vessel at this point. The introduction of the micropipette into the summit of the capillary loop usually does not obstruct flow in the capillary and we may, therefore, assume that the measurement is that of the side-arm or hydrostatic pressure at the middle point of the capillary. Blood flow is often partially or completely blocked by the introduction of the micropipette into the arteriolar limb of the capillary loop. As Krogh showed, the length of capillary between the point of entrance of the pipette and the point of origin of the capillary from the arteriole becomes a side-arm of the manometric system and the pressure measured in this portion of the capillary is the lateral (side-arm) pressure in the arteriole at the point opposite the origin of the capillary. There is an error in determining the level of the right auricle which may be as great as 1 mm Hg in some cases. All in all, it is pretty evident that the error in these measurements of hydrostatic pressure in the capillaries is probably no greater than 1 or 2 mm Hg. This is just the same order as the error in measuring the colloid osmotic pressure. The biological "scatter," as measured by the standard deviation from the mean of our series of measurements of pressures at the venous end of the capillary on normal subjects, is 2.4 mm Hg which is the same as the standard deviation for a series of measurements of colloid osmotic pressures on normal plasmas. As the mean value for a series of measurements of colloid osmotic pressure made upon normal persons is 22 mm Hg and the "mean" hydrostatic pressure measured in the venous end of the capillaries of a series of normal persons is 12 mm Hg the relative variations or relative dispersions of the values obtained from measurements upon normal subjects is greater in the case of the measurements of capillary hydrostatic pressure made in the venous end of the capillary. Moreover, capillary pressure is undoubtedly variable from capillary to capillary depending upon the state of the arteriole to which each is attached, the state of the veins into which each empties, and the state of dilatation or contraction of each capillary itself, whereas the colloid osmotic pressure is constant in any one individual over a considerable period of time. We believe that capillary hydrostatic pressures made according to Landis' method of direct cannulation of the capillary have the same degree of accuracy as measurements of colloid osmotic pressure of the plasma, and the biological "scatter" or "dispersion" of normal values about

the mean of a series of measurements is only a little greater for capillary pressure measurements than for colloid osmotic pressure measurements made upon a series of normal plasmas

Table 1 summarizes our measurements of capillary hydrostatic pressure on 16 normal persons *. The average pressure at the venous end was 12 mm Hg, at the summit of the capillary loop (middle) the "mean" pressure was 20 mm Hg, and the "mean" capillary pressure at the arterial end was 34. Our average pressure at the arterial end and at the summit of the loop is 2

TABLE I
Normal Capillary Pressure Measurements

Case No	V	Capillary Pressure * T	A
1	18		
2	15		
3	12		
4	12	18	30
5	12		
6	12	20	40
7	15		35
8	10		30
9	10		35
10	10		
11	10		
12	15		
13	12		35
14	11		
15	10	20	
16	11	24	35
<hr/>			
Range	10-18	20-24	30-40
Average	12.2	20.4	34.3
P E (c)	1.6		

* = mm Hg
V = venous limb
A = arteriolar limb
T = summit of capillary loop
P E (c) = probable error (corrected for small sample analysis)

mm Hg higher than Landis' average for these points along the capillary pressure gradient. The probable error of the pressure measurements at the venous end of the capillary corrected for small sample analysis is 1.6 mm Hg or a standard deviation of 2.4 mm Hg. These measurements confirm Landis' more extensive normal capillary pressure measurements. They indicate that the method gives consistent results in the hands of other investigators when they have learned the technique.

Table 2 summarizes our capillary pressure measurements in nine cases of right heart failure with edema present. The heart failure in these cases was due to rheumatic or arteriosclerotic heart disease. Moderate to severe edema

* The capillary pressure measurements in this study were made by one of us (I. E.) as part of a thesis in partial fulfillment of the requirements for the degree of Master of Science in Medicine in the Graduate School of the University of Minnesota.

was present at the time of the study in all cases and diuresis had not yet set in, except in case 9. This case, whose capillary pressure in the venous limb was 20 mm Hg, started to have a moderate diuresis during the 24 hour period in which the capillary pressure measurement was made. His urine output on this day was 1800 c c as compared with fluid intake of 800 c c. The patient was at rest in bed during this day, and it is also possible that the capillary pressure dropped somewhat after the pressure measurement was made and within the 24 hour period during which the fluid output was measured. This capillary pressure is undoubtedly the critical point in capil-

TABLE II
Capillary Pressure Measurements in Cases of Right Heart Failure with Edema

Case No	V	Capillary Pressure * T	A
17	25		
18	30		
19	35		
20	25		
21	35		
22	25		
23	40		
24	24		
25	20		
26†	18		
27†	18	25	

* = mm Hg

V = venous limb

T = summit of capillary loop

A = arteriolar limb

† Case 26 Subacute or chronic glomerulonephritis with edema. Serum albumin 2.2, serum globulin 1.4, total plasma protein 3.6. Colloid osmotic pressure 7 mm Hg.

† Case 27 Chronic glomerulonephritis with edema. Serum albumin 2.8, serum globulin 2.7, total plasma protein 5.5. Colloid osmotic pressure 13.5 mm Hg.

lary pressure. With the patient lying in the supine position in bed, edema may or may not develop at this point. Certainly if the patient is up and about with the capillary pressure in the lower extremities increased by the weight of the column of blood between the right auricular level and the limb level, edema will tend to accumulate when the capillary pressure is as high as 20 mm Hg at the venous end. In the other eight cases in this series of measurements the output of fluid was not above the intake. It must be borne in mind that with the accumulation of edema to the visible point there is an increase in the pressure of the extra-capillary fluid which tends to cause absorption of edema if the patient is put in the supine position, unless the capillary pressure in the venous end is at the colloid osmotic pressure level or above. We have three subjects in whom the capillary pressure in the venous limb was 18 mm Hg. One was a normal subject without edema and the other two were cases of glomerulonephritis. These latter two cases had edema, but the colloid osmotic pressure in one of these cases was lowered

to 7 mm Hg and the other to 13.5 mm Hg. In these latter two cases the drop in colloid osmotic pressure alone would favor increased filtration and edema formation.

Our figures are in good agreement with the findings of Krogh, Landis and Turner¹⁰ and Landis and Gibbons¹¹. Using plethysmographic methods these authors were able to detect filtration when the venous pressure was elevated 9 mm Hg above normal. Our measurements, although few in number, would seem to indicate definitely that edema formation takes place in right heart failure when the capillary pressure in the venous limb is increased 8 mm Hg, provided the patient is up and about and is not on a salt free diet. If this patient is then put to bed and fluid and salt intake are restricted, diuresis will tend to develop. When the capillary pressure in the venous end is more than 8 mm above the normal, edema will not tend to disappear until the pressure in the capillaries drops to a point close to 8 mm above the normal capillary pressure.

TABLE III
Capillary Pressure Measurements in Cases of Right Heart Failure with Edema and Following Relief of Edema

Case No	Capillary Pressure *			Remarks
	V	T	A	
28	25	18	30	Marked edema
	12			Edema gone
29	30	15		Marked edema
	15			Edema gone
30	20	24	35	Moderate edema
	11			Edema gone

* = mm Hg
V = venous limb
T = summit of capillary loop
A = arteriolar limb

In the second column of table 3 we show capillary pressure measurements made on three other cases with right heart failure during the period when the patients had edema and diuresis had not yet started, though the patients were in bed with restricted intake of salt and water, and in the third column we show the capillary pressure after diuresis had started and edema was no longer present. It will be noted that in all cases the capillary pressure in the venous end during edema formation is 20 mm or more. After diuresis is started and edema has disappeared, capillary pressures in the venous end of the loop are 15 mm Hg or less. This table shows that during the period of edema formation capillary pressure is elevated 8 mm Hg or more and that after the diuresis starts and edema begins to disappear, capillary pressures have returned to the normal.

We also investigated the capillary pressure in eight cases of marked left heart failure with marked dyspnea, passive congestion of the lungs and cyanosis, but in whom no edema was present and in whom the fluid output

equalled the fluid intake. The results of these measurements are shown in table 4. In all eight cases where severe left heart failure was present but no edema was present, we noted that our measurements indicate that the capillary pressures are well within the normal range. This again shows that even in heart failure with lowered oxygen content of the venous blood, as long as the capillary pressure does not rise 8 mm or more above the normal, no edema will form.

TABLE IV
Capillary Pressure Measurements in Cases of Left Heart Failure (no edema)

Case No	V	Capillary Pressure *	
		T	A
31	12		
32	10		35
33	10		
34	12		
35	12	18	30
36	15		
37	11		
38	11	24	35
Average	12	21	33

* = mm Hg
V = venous limb
T = summit of capillary loop
A = arteriolar limb

In table 5 we show the capillary pressure measurements in four cases in which there was no heart failure present at the time of these measurements but in which the capillaries were at least twice the normal diameter. In other words, no edema was formed when the capillaries were widely dilated as long as the capillary pressures were well within the normal range. Therefore, up to a certain point dilatation of the capillaries is not a very significant factor in edema formation. The reason for this is easy for anyone to see. Unless the capillaries become more permeable to protein, thus causing a colloid osmotic pressure on the outside of the capillary and tending to aid the

TABLE V
Capillary Pressure Measurements in Millimeters Hg in Various Clinical Conditions Associated with Dilated Capillaries without Edema

Case No	Capillary Pressure *			Diagnosis
	V	T	A	
39	12	20	40	Congenital heart disease
40	15		35	Polycythemia vera
41	10		30	Polycythemia vera
42	10			Scleroderma

* = mm Hg
V = venous limb
T = summit of capillary loop
A = arteriolar limb

All cases in the above group had capillaries at least two times normal size

passage of water across the capillary loop and to decrease the absorability at the lower end of the capillary loop, there is just as much increased rate of reabsorption in the capillary in its lower end as there is increased filtration at its upper end in the supine position. These experiments, in our opinion, prove that the hypothesis that edema formation in right heart failure is due to elevated capillary hydrostatic pressure is well founded, and there is no necessity for bringing in any other mechanism than increased capillary hydrostatic pressure to explain the edema formation. The Starling-Schade mechanism of edema formation now comes in the realm of theory and is no longer one of pure hypothesis either in nephritis or in heart failure.

The capillary pressure at the venous end of the tube is 7–8 mm Hg above the venous pressure measured in the basilic vein of the arm. Therefore, when the capillary venous pressure is 20 mm Hg the venous pressure in the arm vein is 12–13 mm Hg or 15.7–17.6 cm of H_2O . Many clinicians have observed that edema of the lower extremities will appear when the venous pressure is 17 cm of H_2O or above unless the patient is put on restricted salt and water intake or put to bed in the supine position. After this work had been finished, and it seemed definitely proved that edema must appear when capillary and venous pressures rise 8 cm of mercury above the normal value, two cases of heart failure, the one a mitral stenosis with tricuspid insufficiency and auricular fibrillation, the other a supposed congenital heart with associated tricuspid insufficiency and auricular flutter, both with large pulsating livers, came into the hospital. These patients had severe dyspnea, markedly enlarged hearts, large pulsating livers, and a high degree of cyanosis but did not exhibit peripheral edema. The venous pressure of the one with mitral stenosis was 20 mm Hg. The pressure at the venous end of the capillary of the finger would, therefore, be at least 27 mm Hg. This observation would seem to overthrow the Starling-Schade concept of balance between colloid osmotic pressure and hydrostatic pressures within the capillaries. If the colloid osmotic pressure in this blood were 22 mm Hg, the capillary pressures throughout the whole capillary would be much higher than this and there would be an excessive continuous filtration of plasma minus the proteins out into the pericapillary regions with the formation of edema. This apparent exception to the rule was soon proved to be an experiment that actually supports the rule because the plasma proteins were determined as 8.9 gm per cent of which 6.0 per cent was albumin and 2.9 per cent globulin. The osmotic pressure as determined in our osmometer was 36.0 mm Hg and, therefore, the capillary pressure at the venous end is 9 mm Hg below the colloid osmotic pressure which is the normal relationship. In the second case the venous pressure in the arm vein was 16 mm Hg corresponding to a hydrostatic pressure of 23 mm Hg at the venous end of the capillaries. If the colloid osmotic pressure were the normal one of 22 mm Hg edema would have to form. But no edema was present. This patient also had an increased plasma protein content of 8.4 per cent, of which albumin was 5.7 per cent, globulin 2.7 per cent, and the colloid osmotic pressure as determined

in our osmometer was 33.0 mm Hg. In this case the colloid osmotic pressure was 10 mm Hg above the hydrostatic pressure at the venous end of the capillaries, which is again the normal relationship. These two exceptions to the rule, when carefully investigated, become excellent proofs that the rule apparently holds that when the colloid osmotic pressure is no more than 2–3 mm Hg above the hydrostatic pressure in the venous end of the capillary, edema tends to form. In both of these cases the degree of anoxemia in the tissues must have been as great as is usual in heart failure with edema formation. The first case has had a high degree of cyanosis for years during which time her auricles have been fibrillating. We know from Kerkhof's⁹ measurements that cases of mitral stenosis with auricular fibrillation have minute volumes at least no greater than 70 per cent of the normal and probably much less even after the heart has been well digitalized. The case of supposed congenital heart with associated tricuspid insufficiency had auricular flutter for many months before these measurements were made and we can infer both from this and the degree of cyanosis that there must have been at least as much anoxemia present as in the average case of heart failure with edema and cyanosis. Yet in neither of these cases was edema present despite the fact that they were both up and about. These two cases, as well as the eight cases of table 4, seem definitely to refute the idea that the degree of anoxemia present in heart failure is sufficient per se to cause edema formation. In the presence of cyanosis, edema does not occur provided the colloid osmotic pressure is 3 or more mm Hg above the capillary pressure at the venous end or 11 mm Hg above the venous pressure in the arm.

Peters¹⁰ and other investigators have shown that the plasma proteins are sometimes reduced in heart disease and in consequence the colloid osmotic pressure must be lowered. As a rule this lowering of colloid osmotic pressure is not great, but it may in rare cases become a prominent factor in edema formation. Therefore, in all rigorous investigations of edema tendency it will be necessary to measure both the colloid osmotic pressure of the plasma as well as the hydrostatic pressure in the capillaries. Colloid osmotic pressure determinations with the Schade osmometer¹¹ are more easily and more quickly carried out than plasma protein determinations. For clinical investigations they can be carried out in a room in which there are no sudden variations in temperature and no air currents. The osmometer acts only as a thermometer for very short periods of time. If the measurements are made at a room temperature of 20° C, it is necessary to correct the value obtained by multiplying by 1.06 in order to get the osmotic pressure at the body temperature of 37° C. The hydrostatic pressure in the capillaries is difficult to measure and time-consuming. But it is not necessary to measure the hydrostatic pressure in the capillaries. The pressure at the venous end of the capillary is approximately 7 mm Hg higher than the venous pressure as measured in the arm vein. For all but the most rigorous investigations the calculation of the capillary pressure at its venous end from the venous pressure measured in the arm is sufficiently accurate. In fact, we can state the

rule for edema tendency, where capillary permeability is not qualitatively changed and where lymph obstruction is not present, as follows. Edema tendency is present when the venous pressure measured in the arm vein is not more than nine millimeters below the colloid osmotic pressure of the plasma. Remembering that the probable error of osmotic pressure determinations is 0.4 mm Hg and that the error in making venous pressure determinations is of the order of 1 mm Hg, we should not expect our measurements to fit the above rule by better than 1–2 mm Hg. Considerable experience in applying the above rule in this clinic has shown that the observations fit the rule in the majority of cases within 1–2 mm Hg.

CONCLUSIONS

1 The cause of edema formation in right heart failure is the rise in capillary hydrostatic pressure. Anoxemia probably plays no essential part in edema formation in right heart failure.

2 A tendency to edema formation develops when the hydrostatic pressure in the venous end of the capillaries rises to within 2 mm or less of the colloid osmotic pressure. If the patient is up and about, if no precautions are taken as to salt and water restriction, and if no diuretics are given, edema will develop.

3 If the colloid osmotic pressure is the normal of 22 mm Hg, edema tendency is present if the hydrostatic pressure in the venous end of the capillary is 20 mm Hg or the venous pressure in the arm vein is 13 mm Hg or 17 cm H₂O.

4 A drop in colloid osmotic pressure of 7 mm Hg or a rise in capillary pressure of 8 mm Hg produces approximately the same edema tendency.

5 Edema tendency is present when the colloid osmotic pressure is not more than 9 mm Hg higher than the venous pressure in the arm.

BIBLIOGRAPHY

- 1 LANDIS, E. M. Micro-injection studies of capillary permeability. III. The effect of lack of oxygen on the permeability of the capillary wall to fluid and to plasma proteins, *Am J Physiol*, 1928, lxxxiii, 528.
- 2 STARLING, E. H. The fluids of the body, 1909, Keener, Chicago.
- 3 STARLING, E. H. On the absorption of fluids from the connective tissue spaces, *Jr Physiol*, 1895–96, xix, 312.
- 4 SCHADE, H. Ueber Quellungsphysiologie und Oedementstehung, *Ergebn d inn Med u Kinderh*, 1927, xxxii, 425–463.
- 5 KIRKHOF, A. C. Plasma colloid osmotic pressure as a factor in edema formation and absorption, *Ann Int Med*, 1937, xi, 867.
- 6 LANDIS, E. M. Micro-injection studies of capillary blood pressure in human skin, *Heart*, 1930, vi, 209–228.
- 7 KIRKHOF, A. C.
- 8 KIRKHOF, A. C.
- 9 KIRKHOF, A. C. Minute volume determinations in mitral stenosis during auricular fibrillation and after restoration of normal rhythm, *Am Heart Jr*, 1936, xi, 206.
- 10 PITTS, J., and PARR, S. A. Serum proteins in heart disease, *Jr Clin Invest*, 1932, vi, 103.
- 11 SCHADE, H. Osmotischer Druck und Oedementstehung, *Ztschr f klin Med*, 1924, c, 370.

INFLUENZA *

By FRANK L. HORSFALL, JR., M.D., *New York, N. Y.*

INVESTIGATIONS of influenza have been beset with serious difficulties since first they were begun. Acute upper respiratory diseases tend to resemble each other very closely and, as is well known, their classification on clinical grounds has not been very successful. One of the chief difficulties is the lack of definite objective signs, except for fever and minor alterations in the appearance of the mucosa of the upper respiratory tract. Unfortunately, there is no sharp line between the symptomatology of a severe common cold, sporadic grippe, and influenza. The manifestations of these symptom-complexes shade imperceptibly one into another, and the difficulties of classifying individual cases as examples of any one of these varieties of acute respiratory diseases are often insurmountable. Various attempts^{1, 2, 3, 4, 5} have been made to establish clinical criteria upon which a diagnosis of influenza might be based, but even among cases in which the etiology of the disease was determined no pathognomonic signs or symptoms were discovered. Almost the only characteristic which serves partially to distinguish influenza from other acute respiratory diseases is a tendency toward epidemicity. However, since epidemics of influenza usually tend to occur at periods when there are also marked increases in the incidence of the other conditions mentioned, even this characteristic loses much of its significance.

An even greater handicap which confronts the student of influenza is the lack of a suitable experimental animal. At the present time ferrets and hamsters are the only known species sufficiently susceptible to infection by the human viruses to be useful. But neither of these species develops a disease which simulates closely that observed in human beings. The hamster fails to show any visible manifestations of infection, and the fact that infection by either of the two known influenza viruses has occurred can be demonstrated only by serological test⁶. The ferret may develop fever and show certain suggestive symptoms, but these have been found to be very unreliable indicators of the presence of infection by human influenza viruses,⁴ and consequently with this species it is also necessary to carry out neutralization tests if accurate information is to be obtained. Although ferrets have been very valuable in studies on the etiology of influenza and their use was directly responsible for the initial discovery of influenza viruses, work with them is difficult, laborious, and expensive. These animals are so susceptible to distemper that a special isolation technic is essential if months of work are not to be rendered futile by an outbreak of this extremely infectious disease. For reasons which are not understood, it has become increasingly difficult

* Read at the Boston meeting of the American College of Physicians, April 25, 1941.

From the Laboratories of the International Health Division of The Rockefeller Foundation, New York.

to recover virus by the use of ferrets from the throats of patients who were shown by serological tests to have influenza A ^{4,5} This suggests either that ferrets are not particularly susceptible to the human virus or that too small quantities of the virus were present in the specimens studied. Whatever the explanation, it is obvious that epidemiological studies based on the recovery of virus from cases of influenza can have at the present time but limited value.

Mice are not susceptible to human influenza viruses. Viruses which become established in this species must first go through a long series of passages before any evidence of infection is produced. Whether or not significant modifications in the virus are induced by this process is unknown. It seems entirely possible, however, that this long process of adaptation may alter other characteristics besides species pathogenicity. It may be of importance to keep this possibility in mind in attempting to interpret results obtained with so-called mouse-adapted strains.

Despite these serious limitations to investigation of influenza, a considerable body of data relating to this illness has been amassed, and it is now known that the epidemic disease may be due to any one of at least three infectious agents. Two of the causes of influenza have been discovered and are known to be viruses. The first, now spoken of as influenza A virus, was described by Smith, Andrewes, and Laidlaw ⁷ in 1933. The second, termed influenza B virus, was described independently and almost simultaneously by Magill ⁸ and Francis ⁹ in 1940. Although no other causal agent has as yet been discovered, the evidence that at least a third agent exists is equally as good as that upon which are based the causal relationships of the two known viruses. During the past year, of more than 850 cases of influenza studied in our laboratory, approximately 30 per cent showed no evidence of infection by either influenza A or influenza B virus and remain, therefore, of unknown cause.

Unfortunately, epidemics of influenza do not seem to be homogeneous as regards the cause of individual cases. In a recent study of outbreaks of the disease in 15 institutions, we found no instance in which evidence could be obtained that all cases studied were due to the same infectious agent. In some institutional epidemics studies of throat washings and sera indicated that at least three etiological varieties of influenza were present simultaneously, while in most institutional outbreaks similar data suggested that at least two distinct kinds of the disease occurred concurrently. Consequently, it seems reasonable at the present time to think that any case in a given epidemic may be caused by one of at least three different infectious agents.

One of the most important problems in influenza is immunity to the disease. Since the therapy of almost all virus diseases is disappointing at best, and since so far no therapeutic agents which significantly modify the course of influenza have been discovered, it is probable that the most hopeful procedure for the control of this disease lies in induced immunity to it. The

fact that the clinical syndrome called influenza includes a number of distinct etiological entities makes it impossible to discuss immunity to these diseases collectively, since it is not yet known that what is thought to apply to influenza A will also be applicable to influenza B or to the influenzas of unknown cause.

For quite obvious reasons it is not feasible to determine whether a given individual is immune or susceptible to influenza A directly. However, it is possible to measure with considerable accuracy the quantity of circulating antibodies against mouse-adapted influenza A virus possessed by different individuals. This has been done under carefully standardized conditions in over 1300 apparently normal persons residing in areas in which epidemics of influenza had not occurred for at least two years. It was found that there were very wide differences in the amount of antibody present in the sera of certain individuals (10). The great majority, over 95 per cent, of adults possessed measurable quantities of antibodies against the virus, but whereas approximately 20 per cent had very small quantities, another 20 per cent had large amounts, and the remaining 60 per cent were distributed in the various antibody ranges between these two extremes.

The marked differences between the quantities of antibodies against influenza A virus possessed by various normal individuals remained of merely academic interest until it was found that they actually were one expression of relative immunity to the disease itself.¹⁰ In more than 200 individuals who contracted proved influenza A a study was made of the serum antibody levels either prior to the onset of the disease or in the first days of the illness before it was likely that additional antibodies would be produced.

A comparison between these results and those obtained in normal individuals has shown that considerably more cases of influenza A occurred in persons with the lowest antibody levels than were to be expected on the basis of the distribution of antibody levels among normal human beings. This suggested that persons with low levels of antibodies against the virus were relatively susceptible to influenza A. Conversely, fewer cases of the disease occurred in persons with high antibody levels than would have been anticipated on the same basis. This suggested that individuals with high antibody levels were relatively immune to influenza A. It is of importance to point out that no critical antibody level was found which assured complete immunity against the disease in any individual case and that a few individuals in the highest antibody range were found to have contracted influenza A.

The evidence that there was a definite correlation between high antibody levels against influenza A virus and relative immunity to the disease itself was of considerable importance since it afforded a rational basis upon which to attempt prophylactic immunization against influenza A. It seemed probable that if it were possible to increase antibodies against the virus to sufficiently high levels in a given population, the incidence of influenza in an epidemic might thereby be reduced.

An attack of influenza A tends to increase antibodies against the virus

markedly during convalescence. This fact is utilized in establishing an etiological diagnosis by laboratory tests¹¹. Unfortunately, the high antibody levels achieved during convalescence do not persist indefinitely, but rather rapidly decrease with time. On the basis of antibody studies carried out at successive intervals after the disease, it seems probable that one attack of influenza A did not result in an enduring immunity and that at least 60 per cent of the cases studied could have been reinfectd by the same virus within one year of their illness¹². This deduction has not yet been verified directly since so far there has been no opportunity to study two attacks of influenza A in the same individual. If, as seems likely, the disease itself does not confer lasting immunity, it is highly improbable that any artificially induced immunity would possess any more durable quality.

It has been shown^{13, 14} that the parenteral injection of active or inactivated influenza A virus stimulated the production of increased quantities of specific antibodies although no clinical illness was produced. This fact has been utilized as a basis for attempts at prophylaxis against the disease. Various kinds of vaccines have been used, and groups of vaccinated and control individuals have been followed through epidemics of influenza. The results have been contradictory in that while some investigators^{15, 16} found reductions in the incidence of clinical influenza among vaccinated persons, others^{2, 17} observed no significant diminution in the frequency of the disease following vaccination.

Recently a vaccine, somewhat different from those previously tried against influenza A, was developed¹⁸. This vaccine was prepared from chick embryos inoculated with both influenza A virus and the X strain of canine distemper virus. Earlier experiments had demonstrated that a complex vaccine of this kind was very effective in immunizing ferrets against experimental influenza A¹⁹. After it was found that the complex vaccine stimulated the production of considerably more antibodies against influenza A virus than any of the other vaccines tested in human beings,¹⁸ an effort was made to determine whether this vaccine would actually produce any significant degree of immunity against the disease itself.

Large groups of persons in various institutions in different parts of this country were given a single subcutaneous injection of the complex vaccine during last fall. Somewhat larger groups in the same institutions were left as unvaccinated controls. Four months after the vaccine had been given, outbreaks of influenza occurred in a number of these institutions. Because it had been found that the etiology of influenza was diverse and since the vaccine was directed only against influenza A, it was considered essential to determine by laboratory tests the etiology of as many cases as possible in both the control and the vaccinated groups. Without the information gained by this extensive study it seemed impossible to make any accurate assessment of the possible efficacy of the vaccine as a prophylactic agent against influenza A.

Almost all of the laboratory studies on throat washings and sera obtained from cases in these outbreaks have been completed. It was found that there were wide differences in the proportion of cases of influenza in the control groups which showed evidence of having been infected by influenza A virus in various institutions. For example, in one institution only 53 per cent of the clinical cases were of this variety, while in another 92 per cent of the cases were caused by this virus. Although lots of vaccine of approximately equal antigenic potency were used in each of these institutions, there was considerable variation in the results observed in various institutions. In one institution there was no difference between the incidence of influenza A in the control and vaccinated groups. In all the other institutions studied, however, the incidence of this disease was somewhat lower among vaccinated persons than among control individuals. These reductions ranged from a 30 per cent to a 90 per cent decrease in the occurrence of influenza A when compared with the incidence of the same disease among the controls. Considered collectively, it was found that influenza A had occurred in about 6 per cent of the control individuals and in about 3 per cent of the vaccinated individuals of these institutions. This indicates that a decrease of approximately 50 per cent in the incidence of the disease was observed among the vaccinated groups.

Obviously these results do not indicate that a satisfactory and trustworthy immunizing agent against influenza A has been found. On the other hand, the reduction in incidence observed is not negligible and suggests that at least a step, however small, has been made in the direction of the eventual control of this disease. Furthermore, the results obtained tend to confirm the available evidence concerning the relationship between high antibody levels and relative immunity to influenza A and therefore may serve to point the way toward more effective prophylaxis. It seems possible that should a vaccine of considerably greater potency become available and should this improved vaccine increase specific antibodies to even higher levels, somewhat more striking reductions in the incidence of influenza A might be expected to result from its administration. Although these are intriguing problems for the future, it should be emphasized again that influenza A is merely one etiological variety of influenza. Until such a time as those other unknown causes of the disease are discovered, it will hardly be possible to develop satisfactory prophylactic measures against epidemics of influenza as such.

REFERENCES

- 1 FRANCIS, T, JR, MAGILL, T P, BECK, M D, and RICKARD, E R. Studies with human influenza virus during the influenza epidemic of 1936-1937, *Jr Am Med Assoc*, 1937, **cix**, 566-569.
- 2 STUART-HARRIS, C H, ANDREWES, C H, and SMITH, W. A study of epidemic influenza with special reference to the 1936-7 epidemic, *Med Research Council, Special Report Series No 228*, 1938, His Majesty's Stationery Office, London.

- 3 FRANCIS, T, JR Epidemic influenza Studies in clinical epidemiology, ANN INT MED, 1939, xiii, 915-922
- 4 HORSFALL, F L, JR, HAHN, R G, and RICKARD, E R Four recent influenza epidemics An experimental study, Jr Clin Invest, 1940, xix, 379-392
- 5 STUART-HARRIS, C H, SMITH, W, and ANDREWES, C H The influenza epidemic of January-March, 1939, Lancet, 1940, i, 205-225
- 6 TAYLOR, R M Detection of human influenza virus in throat washings by immunity response in Syrian hamster (*Cricetus auratus*), Proc Soc Exper Biol and Med, 1940, xliii, 541-542
- 7 SMITH, W, ANDREWES, C H, and LAIDLAW, P P A virus obtained from influenza patients, Lancet, 1933, ii, 66-73
- 8 MAGILL, T P A virus from cases of influenza-like upper respiratory infection, Proc Soc Exper Biol and Med, 1940, xlv, 162-164
- 9 FRANCIS, T, JR A new type of virus from epidemic influenza, Science, 1940, xcii, 405-408
- 10 RICKARD, E R, LENNETTE, E H, and HORSFALL, F L, JR A comprehensive study of influenza in a rural community, U S Pub Health Rep, 1940, lv, 2146-2167
- 11 FRANCIS, T, JR, MAGILL, T P, RICKARD, E R, and BECK, M D Etiological and serological studies in epidemic influenza, Am Jr Pub Health, 1937, xxvii, 1141-1159
- 12 HORSFALL, F L, JR Present status of knowledge concerning influenza, Am Jr Pub Health, 1940, xxx, 1302-1310
- 13 ANDREWES, C H, and SMITH, W Influenza further experiments on active immunization of mice, Brit Jr Exper Path, 1937, xviii, 43-55
- 14 FRANCIS, T, JR, and MAGILL, T P The antibody response of human subjects vaccinated with the virus of human influenza, Jr Exper Med, 1937, lxxv, 251-259
- 15 STOKES, J, CHENOWETH, A D, WALTZ, A D, GLADEN, R G, and SHAW, D R Results of immunization by means of active virus of human influenza, Jr Clin Invest, 1937, xvi, 237-243
- 16 STOKES, J, MCGUINNESS, A C, LANGNOR, P H, and SHAW, D R Vaccination against epidemic influenza with active virus of human influenza, Am Jr Med Sci, 1937, cxiv, 757-768
- 17 TAYLOR, R M, and DREGUSS, M An experiment in immunization against influenza with a formaldehyde-inactivated virus, Am Jr Hyg, 1940, xxxi, 31-35
- 18 HORSFALL, F L, JR, LENNETTE, E H, and RICKARD, E R A complex vaccine against influenza A virus Quantitative analysis of the antibody response produced in man, Jr Exper Med, 1941, lxxiii, 335-355
- 19 HORSFALL, F L, JR, and LENNETTE, E H A complex vaccine effective against different strains of influenza virus, Science, 1940, xci, 492-494

THE PRINCIPLES UNDERLYING THE TREATMENT OF CARDIOVASCULAR SYPHILIS *

By U J WILE, M D , F A C P , *Ann Arbor, Michigan*

FROM the first therapeutic efforts to effect cure to the present moment, the treatment of syphilis has been in a state of perpetual flux. The turnover in the treatment formulae is so rapid that almost every decade sees new methods, newer drugs, superseding those hailed as the last word and the accepted dicta of the preceding like period.

Biological, pathological and bacteriological studies of the past quarter century have led to a much broader concept of the pathology of syphilis and have projected into its clinical aspects many systemic syndromes previously believed to be of other etiology. These numerous entities affecting the osseous, the gastrointestinal, but more particularly, however, the neurological and cardio-vascular systems, have diversified and influenced the various accepted treatment formulae.

For early syphilis in its septic period, and for the many-sided cutaneous and mucous membrane lesions and relapses we may with few qualifications accept standard treatment formulae. When, however, we approach the field of late syphilitic sequelae, particularly those affecting such vital structures as the viscera and the nervous system, standardized treatment must be modified or even replaced by therapeutic efforts directed to the particular system involved and the degree of involvement present.

The therapeutic approach to system syphilis is further modified by the immediate type of the pathologic changes present. Late syphilitic disease wherever found is characterized by two distinct types of lesions, either one of which, or both, may be present. First are such lesions as isolated gummas and diffuse syphilomatous processes accessible and amenable to therapeutic agents. Lesions of this type may exist in various structures, frequently silent, and even when extensive they may exist without causing any appreciable dysfunction of the affected organ. Of greater importance are the mechanical defects resulting from such lesions, and the replacement of normal and diseased tissues by fibrosis, calcification and other degenerative changes. Lesions of this type are not only uninfluenced favorably by treatment, but because of the weakened structures involved and the toxicity of the drugs used, treatment may make them distinctly worse.

In no structure of the body is this better exemplified than in the cardiovascular system. Where late syphilis has affected the heart and great blood vessels, one is faced not only with the necessity for a careful evaluation of the type of lesion present and the choice of a kind and the amount of drug in-

* Read at the Boston meeting of the American College of Physicians, April 25, 1941

Studies and contributions from the Department of Dermatology and Syphilology, University of Michigan Medical School, Ann Arbor, Michigan

licated, but very frequently one may have to decide that no treatment of a specific nature is indicated

An experience of over 30 years with a large number of the variegated types of cardio-vascular syphilitic disease, and stimulated more by earlier mistakes than by successful procedures, I have come to the firm belief that one cannot postulate definitely as to the management of this large group as a whole but, guided by certain underlying principles, each case from its therapeutic and prognostic outlook, must be regarded as an individual problem. A definite plan, therefore, of treatment for the syphilitic heart and aorta cannot be axiomatically laid down

The need for individualization and careful appraisal of each case is at once evident if we review briefly the factors which must be considered. Of almost equal weight in this respect are such data as the age of the patient, the duration of the infection, the background of previous treatment or its absence, the type of the lesion present, the existence or preexistence of decompensation or failure

While we are considering, for the most part, the treatment of the late cardiovascular sequelae, attention should be drawn to the fact that in rare instances involvement of a more or less serious nature may occur precociously as a manifestation of the earlier period. Cases of this kind represent a small, little recognized, and relatively unimportant group. In a very small number of personal observations I have seen arrhythmia, tachycardia, heart block and sudden attacks of syncope in the exanthematous period of the disease which would seem to have indicated early involvement of the myocardium. Sudden death from heart failure has been recorded in a small number of such cases. It would seem not unlikely that involvement of this type may be the result of spirochetal invasion in structures previously damaged from other causes. From the few cases of this type observed, no especial treatment appears to be indicated and the therapeutic response to general systemic measures as laid down for early syphilis, plus bed rest, has been satisfactory

The large group of cases of syphilitic cardiovascular disease may be separated into four distinct groups for special consideration. *First* cases with signs and no symptoms which have had previous energetic treatment directed to their constitutional infection. *Second* cases in which treatment has been energetic early, but in which definite cardio-vascular dysfunction exists. *Third* cases with signs and no symptoms in which inadequate or no previous treatment has been given. *Lastly* cases with both signs and symptoms in which the treatment has been absent or inadequate. To these four groups, a fifth may be added in which symptomatic and asymptomatic cardiovascular disease exists with other predominant visceropathies

In the first group, many of whom represent people in late life with fully compensated lesions, the physician is frequently justified, even in the presence of serological evidence and physical signs, to withhold all treatment. The

majority of such cases are those of well compensated aortic regurgitation and also included in them are a few cases of subclinical aortitis and diffuse aortic dilatation. I have seen many such cases in people of advanced years endlessly and vainly treated in a futile effort to reverse a positive blood test. In this type the continuous barrage of heavy metals and particularly of arsphenamines, may do more harm than good. Such overtreatment indicates a failure properly to evaluate and appraise the individual factors present.

In the second group, those who have been energetically treated before the onset of clinical cardio-vascular disease, I would go even further and state rather categorically that during the stage of decompensation or failure, such cases should seldom, if ever, receive treatment directed to their syphilitic infection. The immediate problem in these cases is not the treatment of active syphilomata, but is one of heart failure, the result of degenerative changes which cannot be appreciably influenced by treatment directed to the old syphilis.

The most favorable cases from the standpoint of therapeutic response following judicious anti-syphilitic treatment, are those included in group three in which cardiovascular disease exists with signs and no symptoms and in whose background there has been inadequate, or no treatment. To what extent the degenerative changes in these cases are inhibited or slowed down by treatment, to keep the lesions asymptomatic, is difficult to determine. No one, however, who has seen such cases in large numbers can fail to be impressed by the fact that many remain stationary, their physical signs remaining constant or even occasionally changing for the better. Dysfunction and failure in such cases seem definitely postponed. The benefit derived by such patients from a non-intensive, but continuous, form of treatment must be due in part to the absorption of syphilitic residua in other parts of the body than in the circulatory system, as well as from the effects of the treatment upon syphilitic residua in the appreciably affected organs. The presence and persistence of syphilitic foci remote from the heart must be recognized as a contributory factor in the ultimate failure in untreated cases.

In the fourth group, which includes those cases which have been inadequately treated early and in which definite cardiac dysfunction exists, the physician is faced with a very delicate therapeutic problem. As in the second group, such cases should seldom, if ever, be treated for syphilis during the stage of their decompensation. When, however, compensation has been restored, following rest and measures directed toward the immediate mechanical defect, judicious treatment on conservative lines is occasionally of unusual benefit. Here again such beneficial effect must be ascribed in part to the response of the remote syphilitic lesions in other parts of the body. With regard to the specific remedies to be employed, I believe the arsphenamines, generally speaking, have little or no place in the treatment of cardio-vascular disease. Occasional cases may be markedly benefited when small doses of these drugs are combined with the heavy metals and the iodides. I am

quite convinced, however, that a plan of treatment, based upon the heavy metals together with rest and iodides, has resulted in an equally large number of successfully treated cases with fewer unhappy results than occur with the arsphenamines. A series of unfortunate experiences in which I had seen the intensive use of the arsphenamine actually produce dysfunction and not infrequently death, leads me to advise against them in cardio-vascular syphilis.

However, with the introduction of tryparsamide and its suggested use in neuro-syphilitic disease, I was early convinced of its singular beneficial effect in certain cases of cardio-vascular syphilis, especially in occasional early aortitis and early aortic dilatation. Although this drug has failed to produce all of the expected happy results in neuro-syphilitic disease for which it was intended, it seems to have an extraordinary tonic effect and its judicious use is occasionally attended with a remarkable improvement in color, strength and weight, so that it merits consideration together with the heavy metals where treatment is indicated.

SUMMARY

- 1 The fundamental principles governing the treatment of cardio-vascular syphilis embrace the careful appraisal of each case with regard to the therapeutic response which might reasonably be expected from the type of lesion present.

- 2 Cases in which failure is present should receive treatment no different from that given heart failure from other causes.

- 3 Cases most favorably influenced by anti-syphilitic treatment are those in which physical signs exist without symptoms, and in which there has been little or no previous anti-syphilitic therapy.

- 4 Asymptomatic cases in which treatment directed toward syphilis has been energetic in earlier years, may often be singled out as patients who need no treatment whatever.

- 5 The beneficial effects of anti-syphilitic treatment upon cardio-vascular syphilis are in a measure the result of the treatment with the drugs of choice upon subclinical syphilitic lesions in parts of the body remote from the heart itself.

- 6 Intensive treatment, such as is given in early syphilis, is seldom indicated in the late cardio-vascular sequelae. Although beneficial results may be noticed with conservative arsphenamine therapy, the heavy metals, generally speaking, are considered safer and productive of equally satisfactory therapeutic response.

HYPERTENSIVE HEART DISEASE OF 10 TO 20 YEARS' DURATION; REPORT OF 11 CASES *

By NATHAN FLAXMAN, M D , *Chicago, Illinois*

It has gradually become recognized that many persons with heart disease may live long and active lives ¹ This seems to apply especially to cases of coronary artery and hypertensive heart disease Isolated long-lived cases of the former etiology have been reported from time to time, but only one article, that of Janeway,² mentions many long-lived hypertensive patients In this classic treatise on hypertensive heart disease, Janeway ³ included 51 patients living more than 10 years from the onset of the first important symptoms Both Riesman ⁴ and Fahr ⁵ stressed the fact that the life expectancy in hypertension is much longer than most physicians are accustomed to believe

In a previous study on the course of hypertensive heart disease ⁶ it was noted that a significant number of patients, although very small in comparison with the remainder, had lived or were living five to 20 years after the appearance of the first symptom, and a lesser group had lived or are living five to eight years after the occurrence of congestive heart failure In another study ⁷ the story of a known hypertensive of 22 years' duration was cited; this man had become decompensated four years previously and at this writing has had hypertensive heart disease over 26 years

TABLE I
Duration of Hypertensive Heart Disease

Years	No	%
10	2	18.2
11	1	9.1
12	4	36.3
15	1	9.1
16	1	9.1
19	1	9.1
20	1	9.1
Average—13.7 years		

Recent optimistic reports on the results obtained with so-called specific surgical treatment for essential hypertension have failed to take into account the fact that some hypertensive patients live many years without such operations To emphasize this fact, the present report includes the case histories of 11 patients with hypertensive heart disease who lived 10 to 20 years (average 13.7 years) after the onset of cardiac symptoms (table 1) In most instances the exact duration of the high blood pressure was not known,

* Received for publication April 5, 1941

From the Department of Medicine, Loyola University Medical School

however, it may be assumed that in all cases the hypertension was present before failure of the hypertrophied heart occurred. There were five males and six females whose ages varied from 25 to 70 years (table 2). Five had regular sinus rhythm, four had auricular fibrillation, the tenth had a bundle

TABLE II
Age Groups at the Onset

Ages	No	%
25-31	1	9.1
31-40	3	27.3
41-50	2	18.2
51-60	3	27.3
61-70	2	18.2
Totals	11	100.0

branch block, and the eleventh had multiple ventricular extrasystoles. Apparently neither the cardiac rhythm nor the age group had any particular influence on the longevity of these hypertensive patients.

TABLE III
Age Groups at Death

Ages	No	%
41-50	2	18.1
51-60	3	27.3
61-70	3	27.3
71-76	3	27.3
Totals	11	100.0

CASE REPORTS

Case 1 S. K., a housewife, first learned that she had high blood pressure at the age of 56. When she was 62 she began to have increasing dyspnea. During the pre-cardiac stage her blood pressure varied from 220 mm Hg systolic and 160 mm diastolic to 160 mm systolic and 110 mm diastolic. The transverse cardiac diameter gradually increased from 12 to 17 cm. She took digitalis, as prescribed for the left ventricular failure, did light housework only, and got along very nicely for many years. Eight years later, at the age of 70, congestive heart failure and auricular fibrillation appeared. The blood pressure dropped to 140 mm Hg systolic and 90 mm diastolic. She died at the age of 72 with generalized anasarca. An autopsy revealed eccentric hypertrophy of the heart, which weighed 570 grams, cardiac cirrhosis, marked passive congestion and a sugar-coated spleen, hydrothorax, ascites, and passive congestion of the kidney, stomach, and intestines.

A known hypertensive of 16 years' duration, this woman lived 10 years' after the onset of cardiac failure.

Case 2 J. K., a white male retired by the depression of the last decade, complained of marked dyspnea at the age of 64. Physical examination revealed a blood pressure of 220 mm Hg systolic and 120 mm diastolic, and a transverse measurement

of 15 cm. Crepitant râles were present at the bases of both lungs. He responded well to digitalis, limited his activity, and went along fairly well for the next 10 years. Whenever he discontinued the digitalis, dyspnea returned and became a prominent symptom. At the age of 74 he developed a rapid auricular fibrillation which precipitated severe congestive heart failure. He died two days after the onset of the arrhythmia. An autopsy revealed eccentric hypertrophy of the heart, which weighed 625 grams, arterio- and arteriolosclerosis of the kidneys with multiple cyst formation, edema and emphysema of the lungs, chronic passive congestion of the liver, spleen, and intestines, hydrothorax and ascites, and edema of the lower extremities.

Although his high blood pressure was not discovered until he entered the cardiac stage, the hypertension was of much longer duration. He was fortunate enough to live 10 years after the onset of left ventricular failure simply by taking digitalis and limiting his activity.

Case 3 M S, a housewife, complained of dyspnea at the age of 52 years. On physical examination a blood pressure of 190 mm Hg systolic and 130 mm diastolic was noted. The transverse cardiac measurement was 14 cm, and moist râles were present at the bases of both lungs. The liver was 4 cm below the costal margin and tender on palpation. An electrocardiogram showed a rate of 100/min and graphic signs of bundle branch block. She was digitalized and responded nicely. In the next 10 years she developed signs and symptoms of congestive heart failure at various times, but each time responded to renewed digitalis therapy. Repeated electrocardiograms showed a persistent bundle branch block. Finally at the age of 63 severe congestive heart failure developed, the blood pressure remained at 170 mm Hg systolic and 110 mm diastolic, the heart reached a size of 21 cm, and she died within three months. Eleven years after the first cardiac decompensation death occurred due to congestive heart failure.

Bundle branch block, graphically noted in this case of hypertensive heart disease, occurs in about 55 per cent of all cases.⁸ It has no definite diagnostic or prognostic significance in hypertensive patients. The prognosis is that of the underlying heart condition, particularly in relation to the occurrence of congestive heart failure. The important cause of death in hypertensive patients with bundle branch block is congestive heart failure.

Case 4 C C, a door-to-door salesman, complained of dyspnea and swelling of the ankles at the age of 55 years. He was a known hypertensive of two years' duration. On physical examination his blood pressure was 200 mm Hg systolic and 130 mm diastolic and the transverse cardiac measurement was 16 cm. There were impaired resonance and moist râles at the bases of both lungs, and the liver was 3 cm below the costal margin and tender. For the next 10 years he slowly pursued his occupation, took digitalis regularly, but continued to have dyspnea on and off at various times. Repeated electrocardiograms in later years showed only a left axis deviation, except when multifocal ventricular extrasystoles appeared. At the age of 65 auricular fibrillation occurred and he was forced to discontinue work. Edema increased, he became bedridden, and died at the age of 67 of congestive heart failure.

A known hypertensive at the age of 53, this man had the first cardiac symptoms and signs at the age of 55. Twelve years after the onset of definite heart involvement he died of congestive heart failure.

Case 5. G. G., a white male continually unemployed by choice rather than by circumstances, was first found to have high blood pressure and an enlarged heart with auricular fibrillation when he complained of severe dyspnea after a heavy drinking bout at the age of 35 years. His blood pressure was 170 mm Hg systolic and 104 mm diastolic and the transverse cardiac measurement was 15 cm. Moist râles were present at the base of the right lung. On bed rest and treatment with digitalis the symptoms and the auricular fibrillation disappeared. During the next 10 years he complained of dyspnea on and off, depending on his omission of digitalis and degree of activity, the latter being limited except for occasional sprees. The heart size did not increase, and the blood pressure ranged between 190 mm Hg systolic and 120 mm diastolic and 160 mm systolic and 100 diastolic. Digitalis would relieve the symptoms until the next time. At the age of 45 he again developed auricular fibrillation which persisted until his death two years later.

Here was a young man who had been an alcoholic for 10 years when he became acutely short of breath after a heavy spree at the age of 35. In spite of continued alcoholism he maintained good compensation with digitalis for 10 years. He died of congestive heart failure at the age of 47, twelve years after the onset of the first cardiac symptom.

Case 6. R. E., a housewife, had a hysterectomy for bleeding uterine fibroids at the age of 39 years. At the time of the operation she was a known hypertensive with the common psychic complaints of headache, dizziness, etc. Previous to surgery her blood pressure was 220 mm Hg systolic and 160 mm diastolic, and after the operation all her symptoms disappeared and the blood pressure decreased to 160 mm Hg systolic and 90 mm diastolic. Within a few months after the hysterectomy her blood pressure rose to the pre-operative level and she complained of dyspnea. The transverse cardiac measurement increased from 11 to 16 cm. Impaired resonance and moist râles were present at the bases of both lungs. The liver extended 4 cm below the costal margin and was tender. There was moderate edema of the lower extremities. An electrocardiogram revealed a rate of 102, left axis deviation, and negative T-waves in Leads I and II. She responded to digitalis and took it regularly. Her activity was limited. After 10 years of fair compensation she began to have congestive heart failure regardless of medication. Twelve years after the onset of the hypertensive heart failure she developed a severe generalized anasarca, lingered five months in bed, and died at the age of 51 of congestive heart failure.

This was a comparatively young hypertensive who obtained complete symptomatic relief and a reduction of blood pressure from a nonspecific surgical (hysterectomy) measure.⁹ Within a few months after the operation the blood pressure reached its original level and dyspnea appeared. However, she remained in fair condition for 10 years after the onset of cardiac manifestations and died of congestive heart failure.

Case 7. J. H., a card sharp, was first examined at the age of 47. He was a known hypertensive with a blood pressure of 180 mm Hg systolic and 110 mm diastolic, and a transverse cardiac measurement of 16 cm. There were moist râles at the bases of both lungs, and the liver was 3 cm below the costal margin and tender. The electrocardiogram revealed a rate of 150 and left axis deviation. He was digitalized and became compensated within a week. During the next 10 years he was hospitalized 10 times during attacks of auricular fibrillation with congestive heart failure, and responded to treatment during each attack. The blood pressure varied between 125 mm Hg systolic and 100 mm diastolic and 100 mm systolic and 80 mm

diastolic during these attacks. At the age of 58 he developed a persistent auricular fibrillation, his congestive heart failure gradually became more marked and he died at the age of 59, twelve years after the onset.

This hypertensive male was seen once a year. He traveled about the country and returned to Chicago only when the symptoms became unmanageable, and had to be hospitalized. Although he always denied taking any digitalis while on the road, it was apparent each time that some of the drug had been taken in the intervals between the attacks of auricular fibrillation each year. On each occasion that he had to be hospitalized, it was for a longer period of time than in the preceding year, until the congestive heart failure no longer responded.

Case 8 L R, a housewife, was found to have high blood pressure and a transverse cardiac diameter of 13 cm when she complained of moderate dyspnea at the age of 61. The second aortic heart sound was markedly accentuated, and the liver was 2 cm below the costal margin and tender. As directed, she limited her housework and took digitalis. She was dyspneic at various times during the next 15 years, but took the digitalis regularly. During this period her blood pressure ranged from 240 mm Hg systolic and 130 mm diastolic to 170 mm systolic and 90 mm diastolic. Her electrocardiogram showed a marked left axis deviation and negative T-waves in Leads I and II. At the age of 76, fifteen years after the onset of cardiac symptoms, she developed an acute coronary occlusion which was the cause of death within a week of its onset.

This hypertensive woman went along for 15 years after the first cardiac symptoms were noted and she lived long enough to develop gross arteriosclerotic changes.⁷

Case 9 M W, a housewife, complained of dyspnea and palpitation at the age of 50 years. On physical examination she was found to have a blood pressure of 200 mm Hg systolic and 140 mm diastolic, a transverse cardiac measurement of 15 cm, and auricular fibrillation. Moist râles were present at the bases of both lungs, and the liver was 4 cm below the costal margin and tender. On digitalis the auricular fibrillation disappeared and she became compensated. Later electrocardiograms showed the QRS complexes to be widened, notched and slurred. During the next 15 years she continued to have dyspnea at various times, but always responded to rest and digitalis. Her activity was always limited. Finally at the age of 66 congestive heart failure re-appeared, and three weeks before her death a left hemiplegia occurred. The blood pressure dropped to 130 mm Hg systolic and 70 mm diastolic, the transverse cardiac measurement was 21 cm, and auricular fibrillation was present. Death was due to a second cerebral embolus.

Sixteen years after the first cardiac manifestations appeared, this hypertensive woman died of cerebral emboli. Her first symptoms were accompanied by auricular fibrillation and this did not occur again until 16 years later at the age of 66.

Case 10 N B, a housewife, complained of dyspnea at the age of 25. It was discovered that she had definite high blood pressure but there was no cardiac enlargement. During the next 19 years she complained of dyspnea and developed moderate edema of the ankles at various periods, but always responded to digitalis. Her greatest activity was light housework. She visited every out-patient clinic in Chicago

many times, but she was never hospitalized until five days before her death. Four or five successive generations of dispensary physicians worked her up completely, usually from a kidney standpoint. Throughout this entire period her cardiac rhythm remained regular, and the blood pressure varied from 210 mm Hg systolic and 120 mm diastolic to 170 mm systolic and 110 mm diastolic. The transverse cardiac measurement increased from 9 to 20 cm over a period of years. Finally at the age of 44, nineteen years after the onset, she developed congestive heart failure with generalized anasarca and died in the Cook County Hospital five days after this occurred. An autopsy revealed a marked eccentric hypertrophy of the heart, which weighed 520 grams, mural thrombi in the appendage of the right auricle, passive congestion of the liver, spleen, and lungs, bilateral hydrothorax, arteriosclerotic granulation of the kidneys, and moderate atherosclerosis of the aorta.

In spite of the poor prognosis generally given a 25 year old hypertensive patient, and especially one with cardiac symptoms, this woman went along for 19 years. The arteriosclerotic granulation of the kidneys, which were shrunk considerably in size, attest to the long duration. Had this patient been subjected to any type of surgery for the lowering of blood pressure, the result undoubtedly would have been considered magnificent. Even without surgery she lived 19 years after the hypertension was discovered.

Case 11 G. C., a laborer, complained of severe precordial pain and dyspnea at the age of 34 years, at which time it was noted that he had high blood pressure. He was told that it was an attack of "acute indigestion." However, his symptoms persisted. He worked occasionally, when there was work to be had, but otherwise sat around, smoked his pipe, and lived at peace with his neighbors. For the next 20 years, until his death, he continued to complain of the same symptoms. The blood pressure varied from 210 mm Hg systolic and 140 mm diastolic to 170 mm systolic and 100 mm diastolic, and the largest transverse cardiac measurement was 18 cm. At the age of 49 he had a severe attack of epigastric pain with dyspnea. This was diagnosed as coronary thrombosis and he was kept on absolute bed rest for six weeks. After recovery, for the last five years of his life, he complained of dyspnea, precordial, and epigastric pain, and he was unable to work. At the age of 54, during an attack of acute left ventricular failure,¹⁰ he suffered a fresh coronary occlusion and expired. An autopsy revealed a recent and an ancient thrombosis of the descending branch of the left coronary artery, an ancient organized and calcified infarct in the wall of the left ventricle, an extensive mural thrombus in the cavity of the left ventricle, eccentric hypertrophy of the heart which weighed 890 grams, multiple ancient and recent infarcts in the spleen and kidneys, liquefaction necrosis of an infarct in the spleen, moderate atherosclerosis of the pulmonary arteries, and fibrous obliteration of the pericardial sac.

Although this case was on a hypertensive and coronary basis, it is included because the coexistence of the two conditions is a common experience. The symptoms were mainly on the coronary basis, and the patient had three distinct occlusions of the coronary arteries, one at age 34, a second at age 49, and the last attack at the age of 54 years. In spite of the facts that the patient was only 34 at the time of the first attack, that he was a laborer, and that he continued at this occupation for 15 years, he lived 20 years after the initial attack but was never entirely free from symptoms. The final coronary occlusion, which resulted in his death at the age of 54, occurred during an attack of acute left ventricular failure on a hypertensive basis.¹⁰

COMMENT

These cases are of special interest from the standpoint of longevity. The first significant symptoms of cardiac insufficiency occurred 10 to 20 years prior to death. In most cases the first complaint was dyspnea. These patients were fortunate enough to escape the unpredictable and uncontrollable causes of death in hypertensives for many years. About 35 per cent of hypertensive patients do not reach the stage of severe congestive heart failure. They are carried off by the intercurrent causes of death, cerebral hemorrhage, coronary thrombosis, and uremia.

There are undoubtedly many examples of longevity with hypertensive heart disease which have not been reported. Fahr⁵ cited three cases of long duration, stated that he had other cases, and that he did not believe these cases to be very exceptional. Riesman⁴ stated that he had had under observation a number of hypertensive women who lived many years. In a series of 269 hypertensive heart patients, Murphy, Woods, and Grill¹¹ reported that only two (0.74 per cent) lived 10 years or longer after the onset of cardiac symptoms. Their high mortality may be in part explained by the fact that the patients were of the type seen in charity institutions.

The mental adjustments to heart disease are of the utmost importance. Especially is this true in hypertensive heart disease.⁷ Sprague¹² made special mention of this, as one of the factors involved in disability. In the light of the factors he listed, it is of interest to analyze the 11 cases from that standpoint. Physical incapacity, the first factor, was not too great in these patients because the congestive failure was controlled by digitalis and none had the anginal syndrome. The character of the patient's work, the second factor, was important in only two cases. Six were housewives, two were unemployed, and one was a card-sharp, their work needs no special consideration. The salesman worked 10 years after his symptoms appeared, but he was his own employer and worked only enough to keep going along. The laborer worked 15 of the 20 years at a highly seasonal occupation, it is doubtful whether he worked six months of the year. Other considerations entered into the reasons why these last two patients continued to work. Both had no fear of heart disease as an incapacitating or fatal ailment. The influence of disability insurance, the fourth factor, need not be considered here as none of the patients had any policies. Disability in heart disease depends on two things: the attitude of the patient in relation to his work and activity, and the type and severity of his symptoms as related to necessary effort.

SUMMARY

Eleven cases of hypertensive heart disease in patients who lived 10 to 20 years (average 13.7 years) after the onset of the first cardiac symptoms are reported. They were of all ages from 25 to 70 years and had various

cardiac rhythmic and conduction disturbances, neither factor apparently influencing the longevity

BIBLIOGRAPHY

- 1 WHITE, P D . The immediate and ultimate prognosis in heart disease, Jr Am Med Assoc, 1939, cxii, 2380-2383
- 2 JANEWAY, T C A clinical study of hypertensive cardiovascular disease, Arch Int. Med, 1913, xii, 755-798
- 3 FLAXMAN, N Janeway on hypertension, Theodore Caldwell Janeway (1872-1917), Bull Hist Med, 1941, ix, 505-516
- 4 RIESMAN, D High blood pressure and longevity, Jr Am Med Assoc, 1931, lxxxxvi, 1105-1107, Thoughts on hypertension, ANN INT MED, 1937, xi, 335-344
- 5 FAHR, G The heart in hypertension, Jr Am Med Assoc, 1935, cv, 1396-1400
- 6 FLAXMAN, N The course of hypertensive heart disease I Age of onset, development of cardiac insufficiency, duration of life, and cause of death, ANN INT MED, 1936, x, 748-753
- 7 FLAXMAN, N The course of hypertensive heart disease, in relation to gross arteriosclerosis, Am Jr Med. Sci., 1938, clxxxxv, 638-644
- 8 FLAXMAN, N The course of hypertensive heart disease III Significance of bundle branch block, ANN INT MED, 1938, xi, 1607-1612
- 9 VOLINI, I F, and FLAXMAN, N Effect of nonspecific operations on essential hypertension, Jr Am Med Assoc, 1939, cxii, 2126-2128
- 10 FLAXMAN, N Types of hypertensive heart failure, Internat. Clin, 1941, i, 25-30, Left ventricular failure due to essential hypertension, Jr Lab and Clin Med, 1941, xxvi, 1891-1900
- 11 MURPHY, F D, WOODS, R M, and GRILL, J Hypertensive heart disease—its clinical-pathological manifestations, Minnesota Med, 1937, xx, 627-642
- 12 SPRAGUE, H B Mental adjustments to heart disease, the factors involved in disability, Jr Am. Med Assoc, 1939, cxii, 2384-2385

THE MORPHINE ABSTINENCE SYNDROME, ITS NATURE AND TREATMENT *

By C K HIMMELSBACH, M D , Passed Assistant Surgeon, United States
Public Health Service, United States Public Health Service
Hospital, *Lexington, Kentucky*

DRUG addiction is a condition in which an individual has become sufficiently subject to an effect of a drug that he can no longer exert adequate self-control with regard to its continued use. Consequently, a separation of the patient from the drug is essential to successful treatment for drug addiction, no matter whether it has been established to opiates, marijuana, barbiturates, alcohol, tobacco, caffeine, or to any other drug or combination. The various drug addictions differ from one another in the manner and extent to which they confer tolerance, habituation, and physical dependence. Tolerance is the term used to denote the ability developed by the organism to diminish the effect of a given amount of a drug. Habituation is the term used to indicate the process of psychical conditioning to repeated effects of a drug. Physical dependence is considered to be a state in which certain physiologic processes have become so conditioned to the effects of a drug that its presence is requisite to the maintenance of homeostasis. The development of physical dependence is comparatively slow, and appears to be influenced more by the regularity and rhythmicity of administration than by the amount of the drug or the route employed.

Withdrawal signs and symptoms (referred to collectively as the "abstinence syndrome") occur when drugs are withheld from a patient who has physical dependence. The abstinence syndromes differ with each drug, for example, the abstinence syndrome which follows withdrawal of cocaine is said to consist chiefly of prolonged sleep,¹ while the outstanding manifestation of caffeine abstinence is headache.² The morphine abstinence syndrome, on the other hand, is usually a severe experience which may become so intense as to cause death. It reaches its peak of intensity on the second day after abrupt withdrawal and recedes slowly thereafter (figure 1), occasionally extending into the third week. If, from a "stress and strain" point of view, it is assumed that the stress of withdrawing 200 mg of morphine is the same in each of a group of addicts, the variations in the resultant strain (abstinence syndrome) possibly reflect the degrees to which mechanisms for the maintenance of homeostasis have been affected by the drug. The severity of the abstinence syndrome varies with the intensity of the physical dependence but, as in other illnesses, may be modified somewhat by the con-

* Received for publication October 30, 1940

Presented at the Southern Psychiatric Assoc., Jacksonville, Florida, October 22, 1940

The term "morphine" as used throughout this paper includes the phenanthrene derivatives of opium used in the practice of medicine

dition of the patient and by his attitude For example, the pressor effect of withdrawal will be greater in a patient with hypertension than in one with normal blood pressure Although few patients show all of the abstinence phenomena, to be described, most of them are commonly encountered

ABSTINENCE DEVIATIONS

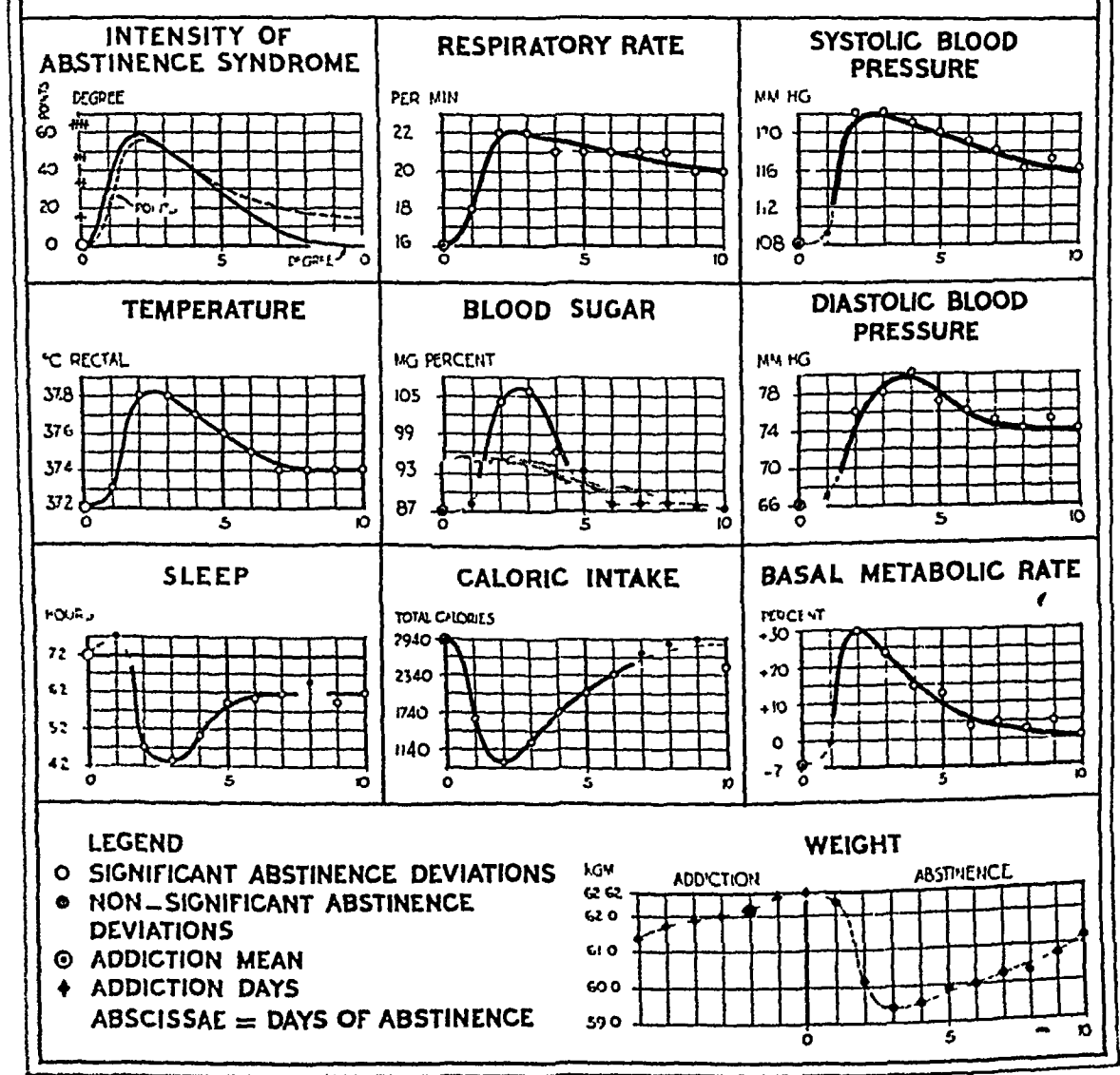


FIG 1

Reproduced through the courtesy of the American Journal of Psychiatry

The purposes of this article are (1) To dispel any doubts as to the existence of an abstinence syndrome, (2) to describe the morphine abstinence syndrome, (3) to discuss simple and reasonably effective measures for alleviation of withdrawal discomfort, and (4) to emphasize that proper man-

agement of the abstinence syndrome, although essential to the treatment of drug addiction, constitutes only its first stage, hence, treatment of the abstinence syndrome should not be considered adequate treatment of addiction

SIGNS AND SYMPTOMS OF ABRUPT AND COMPLETE WITHDRAWAL

General Appearance The general appearance of patients undergoes several changes during the first two weeks of abstinence. During the early part of the first day patients appear drowsy, but later in the day they seem anxious and apprehensive. They become disheveled and careless of the appearance and cleanliness of their persons and rooms. From the latter part of the second day until about the fourth day they appear sick and miserable, their posture is stooped, and they move about in a slouching, shuffling manner. When the intensity of the abstinence syndrome wanes their appearance improves, but they appear weak and tired until about the tenth day of withdrawal.

Weight Weight is lost rapidly following withdrawal. The lowest weight, usually recorded on the second day, represents an average loss of about three kilograms (6.6 pounds). Weight is regained slowly, the addiction level not being reached until the second week of abstinence or later. The weight curve offers an indirect measure of abstinence syndrome intensity and of the recovery process (figure 1).

Eyes The most conspicuous signs referable to the eyes are lachrimation and dilatation of the pupils. Occasionally a patient will complain of double vision. Nearly all patients, if they try to read, complain of some impairment of vision.

Ears Patients tend to be more sensitive to ordinary ward noises following withdrawal than during addiction.

Nose Excessive nasal secretion (rhinorrhea) is a very common sign of withdrawal. Patients sniff, snivel, and sneeze for the first four or five days of abstinence. The sneezing usually occurs in spells of three or more paroxysms at intervals of from a few minutes to several hours. Patients usually find ordinary odors offensive from the second to the fourth day of abstinence.

Tongue Tremor of the tongue is a common withdrawal sign. The majority of patients complain of disturbed taste sense following withdrawal. For example, those who smoke usually find the taste of tobacco offensive. It is a common observation to see a patient light a cigarette, take a puff or two, exclaim over the foul taste, and throw it away in disgust. Measurements of tobacco consumption during addiction and following withdrawal, on a few patients, showed a 90 per cent reduction on the second day with a return to the addiction level by the seventh day of abstinence.

Teeth Addicts' teeth are usually in poor condition. Toothache is more apt to be complained of following withdrawal than during addiction.

Throat The gag reflex is usually hyperactive during the first few days after withdrawal

Mouth Yawning is a common sign of abstinence. It is deeper and more frequent in occurrence than the ordinary yawn of sleepiness, appears early, and continues until the fourth or fifth day of abstinence. Salivation, although rarely marked, is of common occurrence.

Respiratory System The respiratory rate becomes accelerated following withdrawal and does not ordinarily return to the addiction level during the first two weeks of abstinence. Increased secretion of bronchial mucus is common, sputum is produced in increased amounts during the first week of abstinence. Auscultation will often reveal the presence of mucous râles not heard during addiction. Measurements of vital capacity on a few patients during addiction and following withdrawal showed no significant difference.

Cardiovascular System Following withdrawal the heart rate may be increased, decreased, or may not deviate significantly from the rate during addiction. A patient may have bradycardia one day and tachycardia on the next. Arrhythmias have not been encountered, and no significant changes in the electrocardiogram have been found during addiction or abstinence.

The blood pressure (diastolic and systolic) rises following withdrawal. The highest readings, usually obtained on the second day, represent an average increase of 14 mm Hg (figure 1). The blood pressure falls slowly thereafter.

Gastrointestinal Tract Anorexia is a characteristic sign of withdrawal. Measurements of caloric intake show appetite to be poorest on the second day and to return slowly to the addiction level (figure 1). Nausea and vomiting occur in about 60 per cent of strongly addicted patients undergoing abrupt withdrawal. Vomiting may start late in the first day, and does not often persist after the fourth day of abstinence. Diarrhea is as common as nausea and emesis, usually runs the same course, and may become a major symptom. These manifestations indicate hyperactivity of the gastrointestinal tract as regards both secretion and motility. Hypermotility may be observed by auscultation, hypersecretion by the copious amounts of fluid lost through emesis and diarrhea. The vomitus often contains considerable bile. Cramps in the abdomen, alone, or accompanying emesis or diarrhea, constitute a frequent withdrawal complaint.

Skin Gooseflesh (excessive pilomotor activity) is one of the more common signs of abstinence. It appears early in the course of withdrawal, may be transitory, and often persists into the second week of abstinence.

Patients commonly complain of generalized hot and cold flashes, predominantly cold, during the first few days of abstinence. Some patients show distinct flushing of the skin of the face and neck accompanying the "hot" flashes. However, they commonly seek added warmth, many wrap blankets around themselves in "Indian fashion."

Perspiration is another sign of withdrawal. Usually it amounts to little more than palpable moistness of the skin, but occasionally it is excessive.

Patients who have been very restless may develop abraded areas similar to the "mat burns" of wrestlers. This sign is indicative of a severe withdrawal syndrome.

Bones, Joints and Muscles Aching referred to the bones, joints, and muscles is probably the most common symptom of withdrawal. The only sign referable to the muscles is tremor. This is seen sometimes as a fibrillary tremor, and occasionally as twitching.

Glands Glandular activity, which has been more or less suppressed during addiction, responds to withdrawal by greatly increased secretion. This phenomenon is thought to involve the glands of internal as well as those of external secretion. The degree of glandular hyperactivity in elderly patients is not nearly so great as in younger patients. Some signs of withdrawal attributable to excessive secretion are lacrimation, rhinorrhea, salivation, perspiration, emesis, and diarrhea.

Nervous System Anxiety, restlessness, nervousness, insomnia, and hyperreflexia are the predominant deprivation phenomena referable to the nervous system. The degree and character of anxiety, restlessness, and irritability may be influenced by a patient's personality make-up. Sleep is disturbed both in rhythm and amount, the predominant effect being on rhythm. During the first day of abstinence patients tend to sleep more than during addiction. For the next few days sleep is broken and fitful and can best be described as intermittent dozing. Inability to sleep through the night is of major concern to most patients. Sleep equivalent in amount to that of addiction is usually not regained during the first two weeks of abstinence.

Determinations of cerebrospinal fluid pressure were made on a few patients during addiction and the first week of withdrawal. All pressures were within normal limits, and no tendency to rise or fall was noted.

Electrical activity of the cerebral cortex recorded during addiction and following withdrawal has shown no abnormal rhythms.³

Genitourinary System Neither the volume nor the quality of the urine (except for the presence of the drug) is appreciably disturbed during addiction. Following withdrawal, however, the urine volume falls to about 500 c c, then rises to about 1000 c c by the end of the first week, but does not regain the addiction level (of about 1600 c c) during the second week of abstinence. At the height of withdrawal the urine is concentrated and may contain more sediment than during addiction. Increased activity of the reproductive organs occurs following withdrawal.

Metabolism The average basal metabolic rate during addiction is minus 7 per cent. Following withdrawal the basal metabolic rate rises to an average of plus 30 per cent and then falls to zero per cent by the eighth day of abstinence (figure 1). Subsequent change is insignificant.

A low grade fever is characteristic of abstinence (figure 1) The average daily rectal temperature (at 6 00 a m , 2 00 and 7 00 p m) during addiction is 37.2°C On the second and third days of abstinence the average temperature is 37.8° , but falls slowly to 37.4° by the eighth day, and usually levels off at 37.2° during the second week

Blood A brief hyperglycemia of moderate degree occurs during the first week of abstinence (figure 1) Blood inorganic phosphorus drops from an average of 3.3 mg per 100 cc to 2.8 on the second day, and returns to 3.0 by the tenth day of abstinence Blood lactic acid rises from a mean addiction level of 14 mg per cent to 45 mg on the second day, then falls to 25 mg by the tenth day

The average blood sedimentation (Wintrobe tube—read at 60 minutes) during addiction is 20 mm After withdrawal there is a small increase, but this is followed by a progressive decrease to 15 mm in the second week of abstinence Little change in sedimentation occurs thereafter

Studies of blood concentration⁴ showed hydration to be present during addiction A brief relative hemoconcentration occurs during the early part of abstinence, following this the blood becomes hydrated again before returning to normal

Leukocytosis has been reported to occur following withdrawal,⁵ but observations made at this hospital have failed to show a significant increase in leukocytes

COMMENT

The signs and symptoms of withdrawal indicate that the morphine abstinence syndrome constitutes a very real and characteristic illness Although several of these deprivation phenomena can be modified by psychical influences, it is certainly unlikely that this syndrome is entirely psychogenic. The term "functional" can be applied to the abstinence syndrome *if* this word is used in the sense that the deprivation phenomena represent derangements of normal action without demonstrable structural alterations

In certain of its aspects the abstinence syndrome resembles hyperthyroidism, in others, water poisoning⁶, but a more likely cause would appear to be a disturbance affecting the autonomic division of the nervous system, possibly localized in the hypothalamus Grinker and Serota⁷ found that excitation of the hypothalamic region in man caused rise in blood pressure, dilatation of the pupils, perspiration, and hyperemia of the skin Elevation of blood pressure, dilatation of the pupils, hyperpnea, gooseflesh, and hyperglycemia can be cited as examples of sympathetic hyperactivity On the other hand certain abstinence phenomena, such as increased activity of the glands and of the gastrointestinal tract, can be regarded as examples of hyperactivity of the parasympathetic portion An increased liberation of acetylcholine and or an inhibition of cholinesterase could account for manifestations of hyperactivity of both portions of the autonomic division, for acetylcholine stimulates ganglia as well as parasympathetic endings

TREATMENT OF THE ABSTINENCE SYNDROME

Although the majority of addicts find psychic satisfaction in morphine, many resent physical subjection to its powerful influence. This resentment causes them to want treatment, but, since they dread the discomforts of withdrawal, procrastination is characteristic.

It might be assumed that any person who abuses an opiate necessarily develops strong physical dependence upon it, however, although habituation and tolerance seem to develop with comparative ease, physical dependence of truly strong intensity is found in only 20 to 25 per cent of addicts admitted directly to this hospital. One reason for this is thought to be that the adulteration and expense of illicit drugs result in the addict's getting weaker drugs at less regular intervals than are consistent with the development and maintenance of strong physical dependence. As a matter of fact, reduced and irregularly spaced doses of morphine constitute the basis for the better methods of withdrawal treatment.

Accordingly, it seems that the presence of marked or strong physical dependence should be established prior to starting treatment for it. This can be accomplished easily by withholding opiates until signs of withdrawal appear. When the presence of marked or strong physical dependence has been demonstrated, the patient should be temporarily stabilized on the minimal amount of morphine required to prevent withdrawal signs prior to completion of the withdrawal. The amount of morphine required for "stabilization" is usually one and one-half to three grains per day, sometimes four, occasionally more. The total daily dose should be divided into four equal amounts administered subcutaneously. A satisfactory injection schedule is 6 00 and 11 00 a m, and 5 00 and 10 00 p m. Usually before the third day on this program patients will be in satisfactory physical equilibrium. If no serious physical disease exists, the period of stabilization need not exceed one week. During this period history, physical examination and any special examinations can be completed and the decision made as to whether or not further withdrawal can be accomplished safely. Then, too, withdrawal should not be completed until coexisting diseases which might endanger the patient's life (e g, pneumonia, cardiac decompensation) are either cured or brought under adequate control. This period also gives the patient an opportunity to adjust to the hospital routine and to gain confidence in his physician and nurses.

It is convenient to give the last regular dose of morphine at 10 00 p m, and it is usually better to avoid letting the patient know when this is to be done. Patients should not be led to believe that withdrawal will not entail discomfort.

The purpose of withdrawal treatment is to relieve the patient of physical dependence safely, yet without undue suffering or prolongation of treatment. Since ambulatory and home treatments are unsatisfactory as a rule, withdrawal should be attempted in a hospital. Many so-called "specific" treat-

ments have been developed, but often these do more harm than good⁸ The only true "specific" for alleviation of phenomena caused by withdrawal is morphine or one of its derivatives The effect of one "stabilization" dose of morphine on the abstinence syndrome is shown in figure 2 The difference in the areas (A S I point-days) within the mean withdrawal curves of the groups of untreated and treated patients for the first five days shows a reduction of 22 per cent in the treated group Excessive use of morphine will, of course, tend to prolong unnecessarily the abstinence syndrome by giving partial support to the addiction process

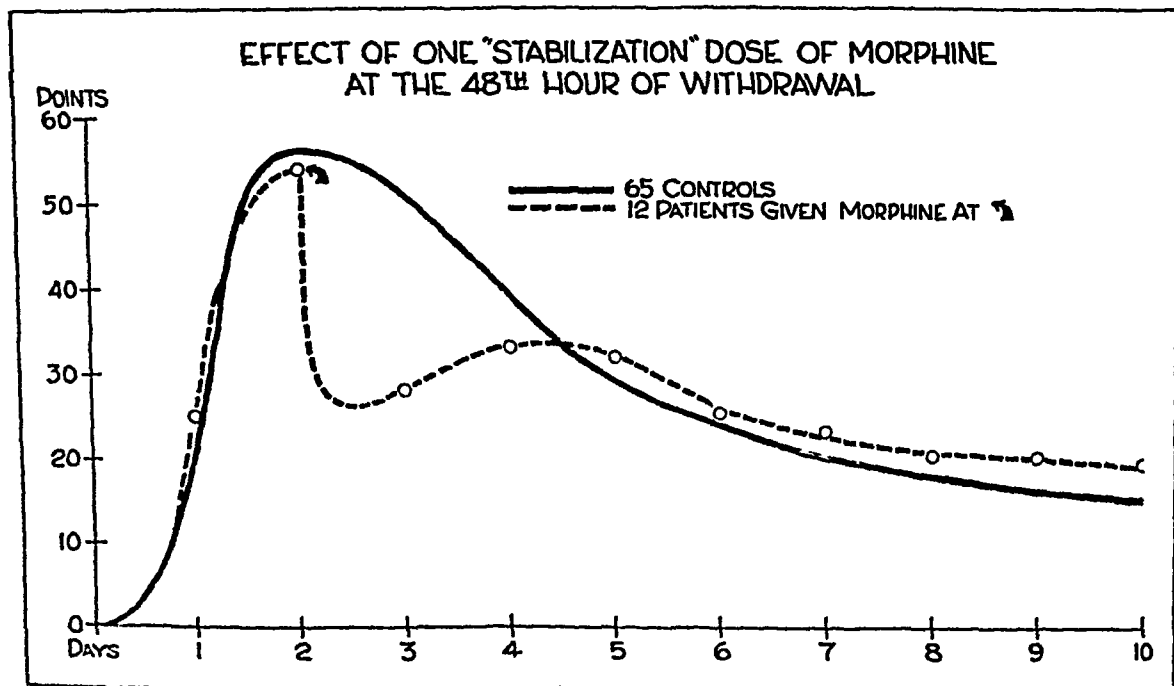


FIG 2

Withdrawal should be rapid rather than abrupt or slow A fixed, pre-arranged schedule of opiate medication has certain advantages over a haphazard method, but should be modified upon appropriate clinical indication A satisfactory schedule is to give an injection of morphine at every third stabilization dose interval for three days, reducing the size of each subsequent dose For example, if the patient was stabilized on one gram of morphine four times a day prior to withdrawal, give one grain of morphine at 5 00 p m on the first day, three-quarters of a grain at 11 00 a m, on the second day, one-half grain at 6 00 a m and one-quarter grain at 10 00 p m on the third day No morphine need be given thereafter, but substitution of codeine for morphine on a similar schedule (figure 3) will facilitate recovery These doses and intervals of opiate administration are consonant with the durations of physical dependence action of morphine and codeine, and of effective withdrawal

On the second and third days following withdrawal, bromides in amounts up to 60 grains three times daily are given to reduce the intensity of nervousness and restlessness. The administration of bromides should be restricted to two days and the sodium chloride intake should be adequate.

Insomnia due to marked restlessness and nervousness has been found to respond better to the administration of paraldehyde than to other hypnotics. Barbiturates for example tend to cause addicts undergoing withdrawal to become confused and delirious.⁹ Ten to 15 cubic centimeters of paraldehyde

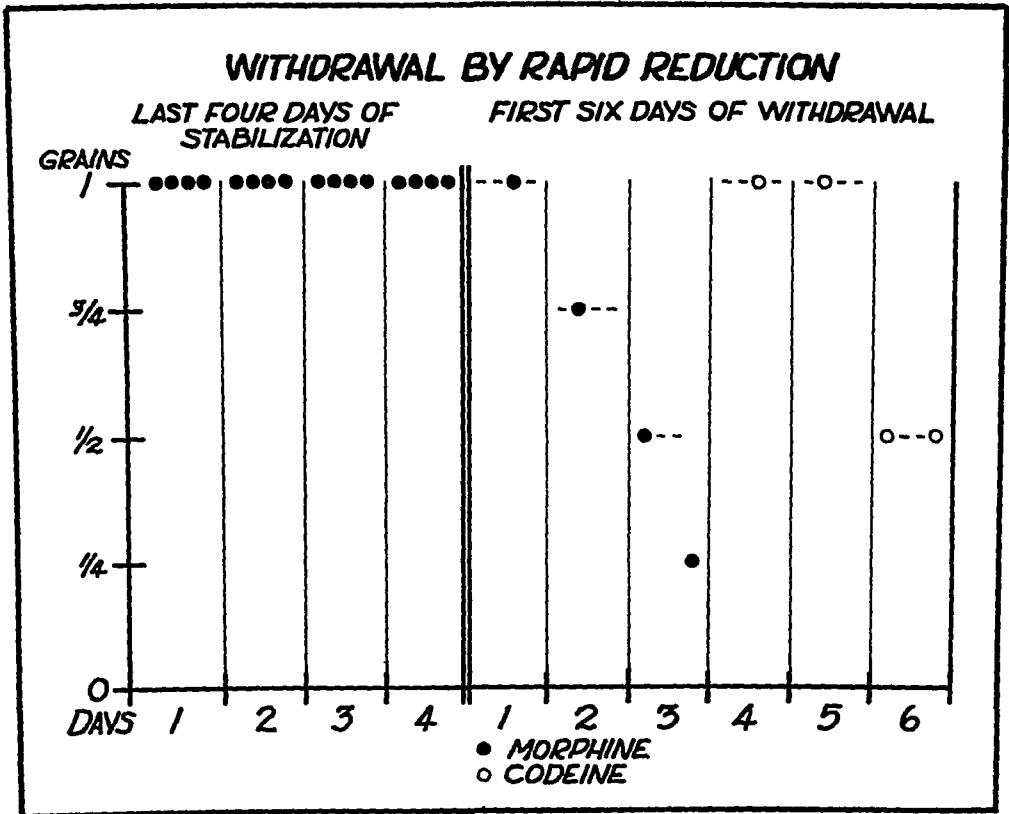


FIG 3

(with 50 to 60 cubic centimeters of warm olive or cotton seed oil) are administered per rectum, after a low cleansing enema, on the second or third night after withdrawal. Sedative flow baths also are effective in reducing restlessness and should be given twice daily on the second, third and fourth days of abstinence. The following technic has proved satisfactory. The patient is placed in a tub filled with warm water (98° F). The water temperature is slowly increased (over a period of 10 minutes) to 102 to 104° F. This temperature is maintained for three to five minutes, then in the next five minutes it is reduced to about 80° F, and the patient is then removed. If the pulse rate goes over 110, or if the patient becomes faint, the temperature of the water should be reduced promptly and the patient removed.

Flow baths and massage will often relieve aches and pains in the legs and back. Massage is more often effective when given directly after a flow bath. Aspirin (five grains) every two or three hours also reduces the intensity of these complaints. Sometimes codeine (one-half grain) by mouth is necessary to relieve severe aches and pains.

Intravenous infusions are given on the second, third and sometimes the fourth days of withdrawal in order to restore the fluid and salt losses. One liter of 0.85 per cent NaCl or of Ringer's solution is given before noon, and one liter of 5 per cent or 10 per cent aqueous solution of dextrose in the even-

TABLE I
Point System for Measuring Abstinence Syndrome Intensity by the
Day (D) or by the Hour (H)

	By Day (D)		By Hour (H)	
	Points	Limit	Points	Limit
Yawning	1	1	1	1
Lacrimation	1	1	1	1
Rhinorrhea	1	1	1	1
Perspiration	1	1	1	1
Mydriasis	3	3	3	3
Tremor	3	3	3	3
Gooseflesh	3	3	3	3
Anorexia (40 per cent decrease in caloric intake)	3	3	—	—
Restlessness	5	5	5	5
Emesis (each spell)	5	—	5	5
Fever (for each 0.1° C rise over mean addiction level)	1	—	1	10
Hyperpnea (for each resp./min. rise over mean addiction level)	1	—	1	10
Rise in a.m. systolic B.P. (for each 2 mm. Hg over mean addiction level)	1	15	1	10
Weight loss (a.m.) (for each lb. from last day of addiction)	1	—	—	—

Total abstinence syndrome intensity score per day or per hour is the sum of the points scored in the (D) or (H) columns, respectively, with due attention to the limits.

It has been found that greater subjective relief is obtained when infusions are given rapidly (15 to 20 minutes) and at room temperature.

Ice collars are used to reduce nausea. Small doses of a short-acting barbiturate (e.g., one gram of "Ipral") often reduce the severity of gastrointestinal symptoms. Diarrhea, if left unchecked, may become distressing, but can be controlled by bismuth subcarbonate in 15 grain doses repeated three or more times daily on the second, third and fourth days of withdrawal.

Liquids, such as egg-nog, milk, and fruit juices are usually tolerated by patients during the first two or three days of withdrawal. Later the liquid diet is replaced by a soft diet, consisting of easily assimilable foods. Patients usually ask for a full regular diet by the fifth to the seventh day.

The attitude of the nurse should be sympathetic and reassuring, yet gently firm. Attention must be given to the minor as well as the major comforts

of the patient. Frequent changes of bed linen and pajamas and the maintenance of neatness and cleanliness are greatly appreciated by patients undergoing withdrawal.

Recorded observations of temperature, pulse, respiration, blood pressure and all withdrawal signs should be made at least every two hours (when the patient is awake) on the first day, hourly on the second day, and three times daily thereafter through the tenth to fifteenth day of abstinence. The patient should be weighed at the same time each morning. With such data the intensity of the abstinence syndrome can be evaluated with sufficient accuracy to follow the progress of the patient adequately and to permit valid comparisons of one form of treatment with another. The objective abstinence phenomena have formed the basis of systems for scoring the intensity of the abstinence syndrome. The system now in use at this hospital is summarized in table 1.

SUMMARY

The morphine abstinence syndrome is a definite clinical entity. Some of the more common signs and symptoms of this syndrome are yawning, lacrimation, rhinorrhea, perspiration, gooseflesh, tremor, dilated pupils, nervousness, restlessness, aching of legs, anorexia, nausea, abdominal cramps, emesis, diarrhea, insomnia, fever, hyperpnea, elevation of blood pressure, and loss of weight. An adequate program for management of the abstinence syndrome consists of a preliminary period of stabilization, rapid reduction of morphine, harmless supplementary measures such as infusions, sedatives, and flow baths, and good nursing with frequent and careful observation. The most important feature of withdrawal treatment is the judicious use of opiates.

REFERENCES

- 1 JEWETT, S. P. Cocain addiction, *Tice, Practice of Med.*, 1935, viii, 53-55
- 2 DREISBACH, ROBERT H. Experimental caffeine withdrawal headache, *Proc. Am. Soc. Pharm. and Exper. Therap.*, 1940, lxi, 283
- 3 ANDREWS, H. L. Some effects of morphine and morphine addiction on the human electroencephalogram (in press)
- 4 WILLIAMS, EDWIN G. Blood concentration in morphine addicts, *Jr. Pharm. and Exper. Therap.*, 1939, lxxvii, 290
- 5 MORAT, D. Le sang et les secretions au cours de la morphinomanie et de la desintoxication, 1911, These de Paris
- 6 ROWNTREE, L. G. The effects on mammals of the administration of excessive quantities of water, *Jr. Pharm. and Exper. Therap.*, 1926, xlix, 135
- 7 GRINKER, ROY R., and SEROTA, HERMAN. Studies on corticohypothalamic relations in the cat and man, *Jr. Neurophysiol.*, 1938, i, 573-589
- 8 KOLB, LAWRENCE, and HIMMELSBACH, C. K. Clinical studies of drug addiction. III. A critical review of withdrawal treatments with method of evaluating abstinence syndromes, *Am. Jr. Psychiat.*, 1938, xciv, 759
- 9 Report of the Mayor's Committee on Drug Addiction, *Am. Jr. Psychiat.*, 1930, \ 433

THE LOCAL AND REGIONAL INJECTION TREATMENT OF LOW BACK PAIN AND SCIATICA ~

By ERNEST A. BRAV, M D, and HENRY SIGMOND, M D,
Philadelphia, Pennsylvania

THE origin of the local and regional injection treatment of low back pain and sciatica dates back to the earliest descriptions of acupuncture. In the Tsin period around 300 A D appeared Huang Fu's classical treatise describing the method of treating painful lesions by the insertion of long needles into the subcutaneous or muscular structures. Churchill's monograph in 1821 reviewed the subject of acupuncture historically, described the technic and presented cases of thoracic and lumbar pain in which it had been used with success. In 1828 a second article gave in detail its use in many additional cases of rheumatism, lumbago, and sciatica. Similar experiences were recorded by many observers who inserted needles deeply along the course of the sciatic nerve. Fayrer described direct puncture of the nerve sheath with relief of tension.

More recently, injection of the sciatic nerve trunk and its surrounding tissues with anesthetic solutions, quinine and urea, chloroform, alcohol, osmic acid and other substances has been a popular method of treatment. The injection of oxygen into the perineural interstitial spaces was suggested by Cordier in 1902. Epidural injection of novocaine, salt solution, camphorated oil, magnesium sulfate, iodized oil, Ringer's solution, oxygen, antipyrine and liquid petrolatum have been widely used with varying results, following the original descriptions by Sicard and Cathelin in 1901. Babcock noted the use of warm water or 2 per cent phenol injected into the muscles of the back in cases of lumbago. Heitzler stated that older authors treated low back and sciatic pain by the injection of morphine into the quadratus lumborum muscles or the painful points along the sciatic nerve. Simple spinal puncture, and intraspinal injections of procaine and alcohol have been recommended in the treatment of sciatic pain.

In the last few years numerous articles have appeared in the literature describing the beneficial effects of injections of various substances into varying anatomic locations, all with the express purpose of relieving low back and sciatic pain, each with a different approach and an individual rationale, but all with amazingly uniform successful results. There is no consistency of substance injected, location attacked or *modus operandi*, but the type of patient treated is relatively uniform, each observer finding to his own satisfaction a logical explanation for the reported success. The reports are as

* Received for publication January 22, 1941.

From the Orthopedic Service of Dr. A. M. Rechtman, Jewish Hospital.

confusing as our present knowledge of the etiology and mechanism of low back pain and sciatica, and evaluation is urgently required if the method is to be retained as a rational form of treatment.

The work of Carnett in 1926 in the diagnosis of intercostal and first lumbar neuralgia and in its differentiation from intra-abdominal and intra-thoracic pain is outstanding as an early influence in the presently favored method of injection for the relief of low back pain. For diagnostic purposes anesthetization of the posterior divisions of the intercostal and first lumbar nerves produced relief of pain and tenderness along the peripheral distribution of these nerves. In 1931 Labat and Greene noted relief of pain by injection of weak solutions (1-3) of 95 per cent alcohol in 1 per cent novocaine into tender areas of the back which were determined by means of a percussion hammer. They found the second and third lumbar and the first sacral areas to be the ones chiefly involved.

Following the work of Carnett, Judovich and Bates observed that many cases of low back pain were due to irritation of the posterior divisions of the twelfth dorsal and first lumbar nerves, with pain and tenderness along the cutaneous distribution of these nerves in the upper gluteal area and, anteriorly, in the groin and upper, inner thigh. They stated that many cases thought to be suffering from sacroiliac and lumbosacral strain were in reality twelfth dorsal and first lumbar neuralgias with referred pain and tenderness along the peripheral distribution of these nerves. Temporary relief was obtained by injection of a procaine solution around the points of emergence of the nerves from their foramina, and permanent relief was often obtained by a combination of procaine and an aqueous extract of the pitcher plant. Irwig injected an area in the lower back midway between the fifth lumbar spinous process and the iliac crest for low back and sciatic pain. He first used 1 per cent procaine, but later recommended a solution of 1 per cent eucupin in oil because of the more permanent effect. Tarsy reported the use of an anesthetic in oil injected into the tender areas of the lower back. Steinbrocker injected a 2 per cent solution of procaine in oil paravertebrally.

Steindler and Luck in 1938 reported the use of procaine solution as a diagnostic agent in low back pain and sciatica. In many cases thought to be due to irritation of the posterior divisions of the spinal nerves, injection of the most tender area of the lower back or buttock produced first an exaggeration of the back and leg pain. With the injection of the solution, the pain and tenderness in the back and leg subsided and previously positive leg signs disappeared. When relief was obtained by injection this was considered as proof of the local site of pathology and of the reflex nature of the sciatic pain. Kellgren noted that pressure on tender points in lumbar myalgia and fibrositis often produced referred segmental pain. This could also be produced by injection of the area with novocaine or salt solution. Novocaine usually gave relief of signs and symptoms and often abolished them entirely.

Gorrell and Copeman reported successful results in lumbago due to fibrositis with the use of nupercaine injection of the tender areas of the lower back. Russetzki, Teneff and Walker used periarthritic and intramuscular injections of novocaine. Haggait reported the use of 1 per cent novocaine injected in quantities of 150 c c around the sciatic nerve at its exit from the notch in cases of sciatica of unknown origin. Haldeman and Soto-Hall injected 20 to 30 c c of 1 per cent procaine into the posterior sacroiliac ligaments in sacroiliac lesions with immediate disappearance of signs and symptoms in almost all of their cases. Douthwaite mentions acupuncture as a method of treatment for sciatic pain, and Bring and Goulden have reported successful results with this method used along the course of the sciatic trunk. The latter observer conducted a galvanic current through the needle.

Injection of procaine directly into the substance of the piriformis muscle is used by Kreuz with startling relief of symptoms of low back pain and sciatica. Gratz, believing that many cases of low back and sciatic pain were due to myosynovitis and adhesions within the fascial planes of the back, buttock and thigh, used insufflation of air into the fascial spaces with considerable success. Forestier used iodized oil which he injected into the local points of tenderness. Copeman suggested that in many cases simple needling of tender areas of the lower back was sufficient to relieve local and radiating pain. In a consideration of the relief of somatic pain by anesthetization, Allen and Tuohy question whether it is the solution or the injection which is responsible.

Galland injected 0.2 to 0.4 c c of a 2 per cent alcoholic iodine solution into the posterior aspect of the sacro-iliac joint with relief of discomfort in cases of low back pain. Harris and Verrall described a case of low back pain and sciatica relieved instantly by injection of alcohol deeply into the tender area behind and below the fourth lumbar transverse process. Thomson injected $\frac{1}{2}$ to 1 c c of thiosinamine compound into the tender nodules of the back in cases of lumbago with good results. Tolderlund recommended the use of intramuscular injections of formic acid. Mayers and Livingston injected a formic acid, sulfur, iodine, camphor preparation into the tender lumbar areas. Smyslov recommended the intramuscular injection of distilled water and hypotonic salt solution into the areas of referred pain.

The questions immediately arising may be stated in the following manner: What is the etiology of the low back and sciatic pain which is relieved temporarily or permanently by the injection treatment? What is the chemical or physical action of the substances injected? What is the significance of the area selected for the injection in any particular case? Is there a psychic factor involved in the success of the injection treatment? And finally, what are the definite uses and limitations of this rapidly growing form of therapy?

In an attempt to convince ourselves of the efficacy of this form of treatment in the routine case of low back and sciatic pain, an unselected series of

70 consecutive patients was thoroughly studied. The examination consisted of a detailed history, complete orthopedic examination including the use of a considerable number of the accepted diagnostic tests, comprehensive radiologic examination of the pelvis and spine, and urine and blood examinations. All patients had nose and throat and dental examinations, the females had gynecologic studies and the males urologic examinations. Those presenting neurologic signs were studied in association with a neurologist, and lumbar puncture and lipiodol studies or air myelograms were performed when indicated. There was no selection of cases except that those presenting conditions obviously requiring surgery or cases in which the back pain was symptomatic of gynecologic or urologic conditions were not subjected to the injection treatment nor included in the series. The patients were a typical group presenting themselves for treatment for concededly orthopedic conditions resulting in low back and sciatic pain.

METHOD OF TREATMENT

After detailed study to eliminate those patients who might have definite requirements for other forms of treatment, there remained 62 patients who we felt were suitable. The paraspinal intramuscular method of injection was used and the patients were divided into three groups. The first group of 28 cases received 10 to 15 c c of 1 per cent novocaine injected into the lumbar muscle mass, unilaterally or bilaterally, depending upon the nature of the complaint. The needle was inserted at a point two inches lateral to the spinous process and directed at a 45 degree angle with the skin toward the posterior division of the lumbar nerve at its exit from the foramen. Injection directly into the nerve was not considered essential. The areas of injection varied, the initial injection being made opposite the first lumbar spinous process, the second opposite the second lumbar and so on down to the fifth. If further injection was required, the next injection started again at the first lumbar area. Only one area was injected at the time of each treatment and injections were given at weekly intervals. This routine was continued regardless of the exact location of the patient's complaints or the type of radiating pain. On numerous occasions it was felt that the first thrust of the needle did not locate the region of exit of the lumbar nerve so that the needle was partially withdrawn and re-inserted. Therefore, there was often a multiple puncture of the fascia and muscle at the time of the individual injection.

The second group of 17 patients was injected in a similar manner but with 10 to 15 c c of normal salt solution. The third group was similarly treated by the insertion of a 2½ inch, 22 gauge needle into the same series of locations, but nothing was injected. The total number of injection treatments was 231. Because some of these were bilateral, the total number of injections was 338. In the individual cases the number of injections varied between one and eleven, the average per patient being 3.7. At no time dur-

ing the course of the injection treatment was any other therapeutic measure employed for the relief of the low back and sciatic pain

CLINICAL DATA

There were 44 females and 18 males. The ages varied between 17 and 73 years. There were three patients in the second decade, seven in the third, 14 in the fourth, 24 in the fifth, eight in the sixth, four in the seventh and two in the eighth. The duration of symptoms varied between one week and 20 years. Three cases were of less than one month's duration, nine were between one and five months, three between six and 11 months, and 47 existed for a year or more. A definite functional element was present in 21 of the patients. The radiologic findings included lumbosacral anomalies in 29 cases, hypertrophic arthritis in 39, atrophic arthritis in two, sacroiliac osteochondritis in one, kyphoscoliosis in 18, and posterior displacement of the fifth lumbar vertebra in four. In four cases the radiograms were normal. A more detailed account of these findings in comparison with a series of painless backs is being reported elsewhere. Referred abdominal or leg pain was present in 27 cases. A history of trauma in relation to the onset of back pain was noted in only eight cases.

CLINICAL DIAGNOSIS

The diagnoses were based on the histories, physical findings and the results of the radiograms and special examinations. There was no direct relationship between the clinical diagnoses and the areas in the radiograms showing the most marked abnormality. The diagnoses were made under two classifications, according to the area involved and to the type of pathology thought to exist. Thirty-two patients had lumbar lesions, 13 lumbosacral, three dorsolumbar, nine sacroiliac and five had combined areas of pathology. In 41 patients, strain or myofascitis was thought to be the underlying cause, in 14 hypertrophic arthritis, in one protrusion of a disc, in one osteochondritis and in five a combination of causes.

RESULTS

The end results were divided into three groups: those with no relief, those with permanent relief and those with temporary relief. By permanent relief is meant at least a full year with absent or markedly decreased complaints. Table 1 represents the results of the injection treatment. In the entire series of 62 cases, 35 (56 per cent) obtained some type of relief. Permanent relief was obtained in 18 (29 per cent).

In the novocaine series, 16 (57 per cent) obtained some type of relief. In 12 (43 per cent) this relief was permanent, whereas in four (14 per cent) the relief was temporary. In the salt solution group, nine (53 per cent) obtained relief. Two (12 per cent) obtained permanent relief, whereas in

seven (41 per cent) the relief was temporary. The use of the needle alone produced some type of relief in 10 (59 per cent). Of these, four (24 per cent) were permanent and six (35 per cent) were temporary.

TABLE I
Type of Relief

	Cases	Permanent		Temporary		Any Type
		Complete	Partial	Complete	Partial	
Novocaine	28	5 (18%)	7 (25%)	0	4 (14%)	16 (57%)
Salt Solution	17	1 (6%)	1 (6%)	4 (24%)	3 (17%)	9 (53%)
Needle	17	2 (12%)	2 (12%)	1 (6%)	5 (29%)	10 (59%)
Total	62	8	10	5	12	35 (56%)

ANALYSIS OF RESULTS

Similar proportions of our patients obtained relief in each of the three groups. The novocaine group presented a definitely higher percentage of permanent relief than either of the others, so that the type of fluid injected may have some bearing on the results. The considerable success with the needle alone, however, is somewhat startling in this respect. Simple relief of tension may be a factor in the relief obtained. Disruption of adhesions by the injected solutions may be a factor but good results were obtained by the needle alone.

The successful cases were analyzed in relation to the results previously obtained by other forms of treatment. All of the 18 cases which obtained permanent relief had had no similar relief from other forms of treatment which included rest, oral and parenteral medication, support, physiotherapy and forms of manipulation. Of the 17 cases with temporary relief, four had had similar relief by other treatment and one patient had comparable reduction of pain from time to time without treatment of any kind.

The results were studied in relation to the emotional state of the patients in the group which obtained relief. Of the 18 patients who obtained permanent relief, 13 were considered normal in this respect, and in five there was a definite neurotic element. The novocaine cases presented a definitely higher percentage of normals in this classification (10 of 12 cases). In all of the eight cases with complete permanent relief, the patients were considered normal. Of the 17 patients with temporary relief, about half were neurotic and the same proportion existed in each of the three injection groups.

It would appear from the comparison of the results with the reaction to former treatment and the emotional type of the individual, that the psychic factor is not of major importance. These patients had considerable opportunity to be impressed by previous forms of treatment including subcutaneous and intravenous medication. The emotional make-up was esti-

mated before the effects of the treatment were known or suspected. The best results were obtained in individuals thought to present an insignificant functional element in their complaints.

The duration of complaints was apparently of tremendous importance in the percentage of successful results. Of 15 patients with complaints of less than one year's duration, 14 were relieved, nine permanently and five temporarily. The one case of short duration which was not benefited was in the salt solution group. Of 47 patients with a duration of complaints of a year or longer, only 21 obtained any form of relief. There were proportionate failures in all of the three injection groups. It would seem then, that in the early cases there is a much better chance for relief by the injection treatment and the type of injection used is again of little importance. It must be noted, however, that the novocaine injections provided a higher percentage of permanent relief.

Comparing the successful results with the clinical diagnoses revealed little difference in the effect of the injections in relation to the type and area of the lesion. In regard to the area of the lesion, there was apparently no difference in the results of the injection treatment. Proportionately good results were obtained in all of the involved areas. In the type classification there was, similarly, some relief in all of the pathologic groups except the protruded disc and osteochondritis. It should be noted, however, that in the 18 cases with permanent relief, 12 were thought to be due to strain or myofascitis, and in the eight cases with complete permanent relief, all except one (hypertrophic arthritis) were in that category.

The results were analyzed in relation to the area of injection in an attempt to determine the importance of the site injected. The cases were here divided into two types: those which had injection only into the first, second and third lumbar areas, and those in which all of the lumbar areas were injected. There were no cases in which the fourth and fifth lumbar areas alone were treated. In general the effects were similar in the two types. In the novocaine cases, the results seemed somewhat better in those in which the upper lumbar areas alone were injected. This was even more definite in the cases which obtained permanent relief.

An analysis of the individual reactions to each injection bears out this impression that the site of injection is of no great importance in determining the results. A similar proportion of patients was benefited by the injections in each of the five lumbar areas. This bears no relation to the final results but seems to favor the non-specificity of any single area of the lumbar region as the site of injection. The effect is that reported by the patient when seen subsequent to the individual injection (table 2).

At the time of injection pain radiated to various areas. In 23 cases it was felt chiefly in the lumbar area; in one case principally in the buttock, in five cases the lumbar region and buttock, in seven cases the lumbar region, groin and anterior thigh, in eight cases in the sciatic distribution and in 18

cases in both the lumbar region and the sciatic distribution. The depth of the injection produced varying effects. In some cases deep injection produced only local pain. In others, radiation of pain was felt while the needle was still superficial to the transverse processes. The pain at the time of injection was not necessarily a reproduction or exaggeration of the patient's original pain. In most cases the complaints and the radiation of pain on injection were dissimilar. The successful cases showed no constant type of radiation of pain on injection, and in these cases there was no relationship between original pain and pain on injection. All locations of radiation were represented in the patients with temporary or permanent relief.

TABLE II
Individual Relief from Each Injection

		Relief	Questionable	None	Total
Novocaine	1 L.	12	12	17	41
	2 L.	12	5	15	32
	3 L.	10	5	5	20
	4 L.	8	4	4	16
	5 L.	2	1	3	6
Salt Solution	1 L.	6	6	11	23
	2 L.	4	5	7	16
	3 L.	5	2	6	13
	4 L.	3	3	3	9
Needle	1 L.	7	4	10	21
	2 L.	8	4	4	16
	3 L.	6	4	2	12
	4 L.	2	3	1	6
Total		85	58	88	231

While most patients complained of pain on injection at a certain area regardless of the site of injection, there were many cases in which different areas of radiation were noted following individual injections. In these latter cases, however, there was no definite pattern of radiating pain produced by the injection of any specific lumbar area. A similar proportion of injections in each of the five areas produced sciatic pain. The same was noted in the production of groin and anterior thigh pain.

Of the 35 successful cases, 10 obtained relief of discomfort immediately or within an hour after injection. In four cases, the relief came in several hours and in 21 no improvement was noted for several days. In general each patient noted relief in a similar period of time after each injection, the exceptional case varying in the time in which relief was obtained. In the successful cases, not every injection was followed by relief, and in the failures, many injections were followed by temporary relief with early recurrence. Thus, of 231 injection treatments, 85 were followed by definite relief, 58 by questionable relief and 88 by no relief.

In the entire series of 62 cases, the immediate effects of the injections on the physical signs consisted of relief of tenderness in 10 cases, improved spinal motion in six cases, improved straight leg raising in two cases, change in Gaenslen sign in one case and change in Ober sign in one case. The relief of tenderness occurred in the novocaine group in eight cases, in the salt solution group in two and from the needle alone in none. The other effects were distributed evenly in the three groups. The Gaenslen and Ober sign changes occurred in salt solution cases.

The signs at the time of the patient's last visit in the successful cases revealed improvement in spinal bending and relief of pain on motion in 18 of 35, decreased tenderness in 17 of 35, improvement in straight leg raising in 7 of 10, loss of Gaenslen sign in 3 of 4, loss of pain in fabere test in 3 of 4, and relief of pain on internal rotation of the hip in two cases. In the failures there was no significant change in the physical signs despite reported temporary relief after various individual injections.

COMMENT

It is not the purpose of this paper to discuss the varied etiology, the poorly understood mechanism or the general therapeutics of low back and sciatic pain. The analysis of the present series, however, may be of service in evaluating the rationale, indications and limitations of the injection method of treatment. The etiology of our successful cases included those due to strain, myofascitis, hypertrophic arthritis, atrophic arthritis and a combination of these factors. Ligamentous, articular, muscular and intermuscular causes of pain would appear to be those best suited to the injection treatment. It is possible that in patients with other basic causes, as for example intraspinal or bone lesions, there are associated ligamentous or muscular changes which may be somewhat improved by the injection treatment. In any discussion of this type of treatment it must immediately be understood that we are dealing with symptomatic therapy, and that, whenever possible, the basic cause of the ligamentous, articular, muscular or intermuscular abnormality should be detected and removed.

The location in the lower back or buttock of the pathologic process responsible for the back and leg pain seems to be of no great importance so far as the efficacy of the injection treatment is concerned. This suggests at once the possibility of mistaken diagnosis and this criticism is not unwarranted. It is possible to be misled by an area of referred tenderness so that a primary lumbar lesion may be thought to be sacroiliac or gluteal in origin. We do not believe, however, that all of our successful cases were due to lumbar lesions. It is possible that the effect is that of relief of a secondary area of pathology or of muscle spasm in the area which is injected.

The mechanism of the relief of discomfort is still problematical. The functional element has been fairly well eliminated. From the various substances which have been used by other observers with considerable success

and from our own experience, it would seem that there is one and only one common factor in all of the cases which have been relieved by the injection treatment and that factor is the needle

The theories quoted by others for their successful results which include effects due to the production of hyperemia, regional shock therapy, interruption of sensory reflex, restoration of vasomotor equilibrium, altered local tissue metabolism or stretching of adhesions would seem fantastic in the light of results obtained by the needle alone. The relief of increased intramuscular or intrafascial tension and edema, or the reduction of muscle spasm, as has been suggested, might, however, offer a reasonable explanation of symptomatic improvement. That this should, in some of our cases, be followed by permanent relief of symptoms and improvement in physical signs is no more readily explained than similar effects reported by others with the use of a host of varying substances.

The site of injection apparently bears no definite relation to the success of the treatment and is not necessarily directly connected with the location of the causative lesion. Patients have been relieved by injection of epidural, intermuscular and perineural spaces, posterior divisions of the lumbar nerves, muscular and nervous tissues and the subarachnoid space, and the injections have varied in location from the lower dorsal region to the lower thigh. In our own series the individual responses of relief obtained and the successful end results were independent of the particular area of the lumbar region which was injected.

The radiation of pain at the time of injection in both the failures and the successful cases bore no relationship to the original complaints. Furthermore, the depth of injection was not constant in the production of radiating pain. The area of injection provoked no constant type of radiation. These observations suggest again the non-specificity of the injection treatment as to location of the causative factor and as to the area at which the injection is made. They further suggest that there is no definite relationship between the area of the causative lesion and the type of radiating pain.

Provided that injections are made under aseptic technic and provided that no harmful or unduly irritating substance is injected, there are no contraindications to the injection treatment. Carelessly used, however, the method is bound to be the cause of faulty diagnosis, delay in adequate treatment and unduly prolonged convalescence. Penetration of the subarachnoid space by the needle must be avoided. The treatment must be recognized as symptomatic and the basic factors tracked down and eradicated. The method should be used only in patients who have had the benefit of a complete physical examination, radiologic studies and the elimination of remote causes of low back and sciatic pain. It should not be used in osseous, intraspinal, pelvic and genito-urinary causes of pain. It should not be used as a shotgun procedure in the case of any patient presenting these complaints. It should not be used as a method of psychotherapy. It should not be used, except as

a temporary measure for the relief of pain, in bone and joint lesions which suggest the application of another form of treatment calculated to influence the *cause* of the complaints

CONCLUSIONS

1 The local and regional injection treatment of low back and sciatic pain is a symptomatic treatment which must be accompanied by measures to alleviate or eradicate the cause of the disorder

2 The treatment offers a possibility of success in cases where discomfort is due to muscular, ligamentous, articular or intermuscular causes

3 The functional element is of no importance in the success of the injection treatment

4 The treatment offers better chance for success in the cases of short duration

5 There is no specific area of the back or buttock in which the injection should be made and the area of injection bears no definite relation to the site of the causative lesion

6 There is no specific palliative or curative substance or solution to be injected

7 There is no logical explanation at hand for the temporary and permanent relief which has been obtained. Relief of intramuscular and intermuscular tension, and diminution of muscle spasm are the most reasonable explanations but there is no available proof

8 The observation that the common factor in the success obtained by various observers with a host of substances in widely varying anatomic locations is the use of a needle, suggests the ancient therapeutic procedure of acupuncture

SUMMARY

1 The history of the local and regional injection treatment of low back and sciatic pain is reviewed

2 A series of 62 consecutive patients treated by this method is presented. All cases were treated by paravertebral deep intramuscular injection. Of 28 cases treated with novocaine, 16 (57 per cent) obtained relief. Of 17 cases treated with normal salt solution, 9 (53 per cent) obtained relief. Of 17 cases treated by the needle alone, 10 (59 per cent) obtained relief. The percentage of permanent relief was somewhat higher in the novocaine series than in the others.

3 An analysis of these results is presented with regard to the substance injected, the area and depth of the injection, the clinical diagnosis, the functional element, the effect of previous treatment, the duration of complaints, the type of pain on injection and its relation to the original pain, the immediate effects of the injection and the alteration in the physical signs.

4 An evaluation of the injection method of treatment is offered, its rationale discussed and its uses and limitations defined.

BIBLIOGRAPHY

- 1 ALLEN, E. V., and TUOHY, E. B. Relief of somatic pain by anesthetization, *Proc Staff Meet, Mayo Clin*, 1940, *xx*, 58-60
- 2 ALLEN, E. V., and PARRISH, R. E. Spinal puncture as a method of treatment for sciatica, *Therap Gazette*, 1918, *xlii*, 381-382
- 3 BANCOCK, W. W. A textbook of surgery, 1928, W. B. Saunders Co., Philadelphia, pp 1367, p 382
- 4 BRING, M. L'acuponcture chinoise dans le traitement de la nevralgie sciatique, *Rev gen de clin et de therap*, 1939, *liii*, 486-487
- 5 CAMUS, H. A. The use of quinine and urea hydrochloride in sciatica and allied conditions with report of cases, *Lancet-Clinic*, 1915, *cxiv*, 57-59
- 6 CARNETT, J. B. Neuralgia of the intercostal and first lumbar nerve, *Pennsylvania Med Jr*, 1929, *xxxiii*, 876-880
- 7 CARNETT, J. B. Intercostal neuralgia as a cause of abdominal pain and tenderness, *Surg, Gynec and Obst*, 1926, *xlvi*, 625-632
- 8 CARRIÈRE, G., and VANVYRTS, J. Sur un cas de sciatique guéri par une injection intrarachidienne de cocaïne, *Nord med Lille*, 1901, *vii*, 139
- 9 CATHILIN. Une nouvelle voie d'injection rachidienne methode des injections epidurales par le procédé du canal sacre, *Comp rend Soc de biol*, 1901, *liii*, 452-453
- 10 DE CIREVILLE. Des injections profondes de chloroforme dans le traitement des sciatiques myélerces, *Bull soc med de la Suisse Rom*, 1876, *x*, 193
- 11 CHURCHILL, J. M. A treatise on acupuncture, 1821, Simpkin and Marshall, London, pp 86
- 12 CHURCHILL, J. M. Cases illustrative of the immediate effects of acupuncture in rheumatism, lumbago, sciatica, anomalous muscular diseases and in dropsy of the cellular tissue, 1828, Callow and Wilson, London, pp 101
- 13 COPEMAN, W. S. C. Fibrositis, *Jr Am Med Assoc*, 1936, *cxvii*, 1295-1297
- 14 CORDIER, M. Emploi des injections gazeuses en therapeutique, *Lyon med*, 1902, *xcviii*, 430-437, 490-498
- 15 DOUTHWAITE, A. H. The treatment of rheumatoid arthritis and sciatica, 1930, H. K. Lewis & Co., London, pp 131, p 110
- 16 FAYRER, J. Puncture of the nerve sheath in sciatica, *Practitioner*, 1886, *xxxvi*, 266-267
- 17 FORESTIER, J. The relief of pains of the locomotor system by local injections of iodized oil with control by x-rays, *South Med Jr*, 1935, *xcviii*, 289-295
- 18 GALLAND, W. I. Low back pain, *Arch Phys Therap*, 1937, *xviii*, 16-25
- 19 GAROFEANO, M., and LABIN, B. Le traitement de la nevralgie sciatique par les injections epidurales de sulfate de magnesium, *Arch med Belges*, 1923, *lxxvi*, 473-478
- 20 GORRELL, R. L. The nupercaine treatment of lumbago, *Tri-State Med Jr*, 1939, *xi*, 2223-2224
- 21 GOULDEN, E. A. The treatment of sciatica by galvanic acupuncture, *Brit Med Jr*, 1921, *i*, 523-524
- 22 GRATZ, C. M. Fascial adhesions in pain low in the back and arthritis, *Jr Am Med Assoc*, 1938, *xi*, 1813-1818
- 23 HAGGART, G. E. Sciatic pain of unknown origin, *Jr Bone and Joint Surg*, 1938, *xx*, 851-859
- 24 HALDEMAN, K. O., and SOTO-HALL, R. The diagnosis and treatment of sacro-iliac conditions by the injection of procaine, *Jr Bone and Joint Surg*, 1938, *xx*, 675-685
- 25 HARRIS, W., VERRALL, P. J., et al. Discussion on sacroiliac pain, *Trans Med Soc London*, 1928-29, *lii*, 82-98
- 26 HAY, A. G. The treatment of sciatica by means of intraneural injections of saline solution, *Practitioner*, 1912, *lxxxviii*, 145-155
- 27 HECHT, D'O. The treatment of sciatica by deep perineural injections of salt solution, *Jr Am Med Assoc*, 1909, *lii*, 444-449

- 28 HERTZLER, A E The nature and treatment of sciatica, *Am Jr Surg*, 1926, i, 200-207
- 29 IRWIG, F Treatment of low back pain, *Indust Med*, 1939, viii, 105-112
- 30 JORDAN, H Erfahrungen mit der epiduralen Antipyrininjektion bei Ischias, *München med. Wchnschr*, 1925, lxxxi, 560-562
- 31 JUDOVICH, B D, and BATES, W Low back pain, *Indust Med*, 1939, viii, 160-165
- 32 JUDOVICH, B D For the relief of pain a preliminary report on a new therapy, *Med Rec*, 1935, cxlviii, 583-584
- 33 KELLGREN, J H A preliminary account of referred pains arising from muscle, *Brit Med Jr*, 1938, i, 325-327
- 34 KREUZ, F P : Unpublished material
- 35 KUZMA, V Camphor oil injections in therapy of sciatica, *Medicina*, Kaunas, 1933, xiv, 719-725
- 36 LABAT, G, and GREENE, M B Diagnosis and treatment of the so-called sciatic neuralgias, *Am Jr Surg*, 1931, xi, 435-451
- 37 MAYERS, L H, and LIVINGSTON, S K The treatment of arthritis and associated conditions, a preliminary report, *Indust Med*, 1939, viii, 3-20
- 38 RUSSETZKI, J La novocaine et le traitement des sciatiques, *Lyon méd*, 1938, clxi, 111-116
- 39 SICARD, A Les injections medicamenteuses extradurales par voie sacrococcygienne, *Comp rend Soc de biol*, 1901, liii, 396-398
- 40 SICARD and COSTE Lipiodol épidual sacro-coccygien, *Bull et mém Soc méd hôp de Paris*, 1924, xlviii, 242-244
- 41 SMYSLOV, G G Therapy of radiculitis and neuromyositis of lower extremities by intramuscular injections of distilled water and hypotonic salt solutions into areas of referred pain, *Klin Med*, 1935, xiii, 1208-1213
- 42 SOLIS-COHEN, S Obstinate sciatica cured by deep injections of osmic acid, *Jr Nerv and Ment Dis*, 1889, xvi, 177-179
- 43 STEINBROCKER, O Local injections and regional anesthesia with procaine solutions for intractable pain in chronic arthritis and related conditions, *ANN INT MED*, 1939, vii, 1917-1939
- 44 STEINDLER, A, and LUCK, J V . Differential diagnosis of pain low in the back, *Jr Am Med Assoc*, 1938, cx, 106-113
- 45 TARSY, J M Treatment of low back pain by regional and local analgesic injections, *Indust Med*, 1939, viii, 186-193
- 46 TFNEFF, S Behandlung der Ischialgie mit periartikulärer intervertebraler Novocaininfiltration, *Chirurg*, 1939, xi, 237-239
- 47 THOMSON, F G . Treatment of pain in lumbago, *Practitioner*, 1934, cxxviii, 274-280
- 48 TOLDERLUND, H Therapy of rheumatic conditions with intramuscular injections of formic acid, *Ugesk f laeger*, 1933, xcvi, 305
- 49 WALKER, J A L Low back pain and sciatica, *Canad Med Assoc Jr*, 1939, xi, 240-247

SCREENING FOR TUBERCULOSIS IN A CIVILIAN POPULATION BY FLUOROGRAPHY *

By BRUCE H. DOUGLAS, M.D., F.A.C.P., and CARL C. BIRKELO, M.D.,
Detroit, Michigan

THE control of tuberculosis must be based on the same general principles that are applicable to the control of all communicable diseases. Since there is no effective means so far developed for immunizing the population against tuberculosis, the efforts to prevent its occurrence must rest largely on limiting the spread of the organism responsible for the cause of the disease. Since bovine tuberculosis has been so well controlled in this country the one remaining important source of tubercle bacilli is the persons who have tuberculosis. It therefore becomes of prime importance to detect as far as possible all the cases of tuberculosis in the community not only for the sake of finding them early when a good chance of recovery exists but also before they have had any opportunity to spread the infection to those about them.

The insidiousness of the onset of tuberculosis either through lack of symptoms at all or the presence of symptoms like those of a cold or other respiratory disease not regarded too seriously by the patient makes it very apparent that if the patient waits until he has really become ill enough to seek his physician's advice he will often have progressed well beyond the early stages of the disease. This, in part at least, has accounted for so many cases failing to be recognized before they have reached a far advanced stage when recovery is more difficult and when they have probably unwittingly been spreaders of infection for some time.

The examination of large groups of presumably well persons for the detection of tuberculosis has therefore come to be looked upon as sound practice since every early case discovered means savings to the individual, the family and the community in lessened hospital care and in less chance of infecting others.

Edwards¹ of New York has shown the usefulness of mass surveys of large groups in uncovering tuberculosis particularly when such surveys are conducted in groups that previous experience has shown have a greater prevalence of this disease than that of the rest of the community.

In searching for tuberculosis it is most important to find the pulmonary cases since they are most likely to be in a communicable state. Although the extra-pulmonary cases of tuberculosis may occasionally be infectious they are much less apt to be so and of course are much less in number than the pulmonary cases. On this basis then survey methods are designed to detect the pulmonary forms of tuberculosis.

* Read at the Boston meeting of the American College of Physicians, April 25, 1941

Everyone is familiar with the use of the tuberculin-roentgen-ray survey technic in which a tuberculin test is used to indicate those who may at some time have been infected with the tubercle bacillus, and the roentgen-ray of the chest was applied to all those reactors to determine whether there might be actual disease present. This method of survey was first extensively used in Massachusetts in the now famous Chadwick Clinics for the discovery of tuberculosis in school children. Although this method has been successfully used for some time, it has been felt by many workers that if a more economical yet reasonably accurate method of roentgen-ray examination could be developed it would be a more practical survey method with less chance of error when applied directly to the whole group without previous tuberculin screening.

Accordingly many efforts have been directed toward producing a less expensive type of roentgen-ray examination, with varying degrees of success. Sensitized paper, the direct fluoroscopic examination, and more recently the photography of the fluorescent image on the fluoroscopic screen using small film of various sizes have been developed to meet the requirement of economy in surveys.

The authors have had the opportunity to use one of the fluorographic methods for the past two years in case finding surveys, the results of which have been very satisfactory.

The method used was that developed by Dr. Hollis E. Potter² in collaboration with the laboratories of the General Electric X-ray Corporation.

This fluorographic method employs a specially built lens in a camera screen unit capable of making a photograph of the fluorescent image on a 4×5 inch film. This size was arrived at after extensive study as being most desirable since it is large enough to be readily interpreted without enlargement and yet small enough to make a real saving in material cost, namely, about one-tenth the cost of the full size film.

The source of roentgen-ray for this type of work must be good. At least a 200 milliamperere tube should be used and even more brilliant films can be taken if a rotating anode tube allowing the use of 400 milliamperes is used since this will allow a greater target-screen distance and a shorter exposure.

Careful checking as to the accuracy of this method by taking films of a large number of patients with both the regular film and the small size revealed an error of 2.6 per cent in failure to detect certain very small lesions. 'This work has been reported in detail elsewhere.' More recently Bridge⁴ in a similar study reported less than 1 per cent error.

Since questionable lesions may be better visualized on a large film such patients may be called back for large films but in the experience of the authors this has not been necessary except in a relatively small number. For example, it was found necessary to call back only 51 persons for re-check on a large film in a consecutive series of 6,104 small films.

These small films can be made rapidly, better than one a minute, which is as rapidly as persons can be prepared for examination and handled conveniently through most clinics

This method has been used now for over a year and a half in the out-patient department of the Herman Kiefer Hospital for the examination of contacts and those suspected of tuberculosis. Over 30,000 such examinations have been made and have proved very satisfactory in determining the presence or absence of pulmonary tuberculosis of an amount necessary to require hospitalization. For the careful work of determining the type of treatment and controlling the progress of the patient in the hospital the small films have not been used since here the utmost of detail is required, often stereoscopic studies, Bucky diaphragm films, or perhaps section roentgenography.

The follow-up of patients discharged from the hospital or sanatorium is also being done at the clinic with the fluorograph. The economy of this examination makes it possible to examine more frequently than was possible with the previously limited number of large films available.

Several groups other than the contacts and suspects examined in the tuberculosis clinic mentioned have been studied on the basis of surveying those whose situation might make them more likely to have tuberculosis than others. One of the first of these groups in which continuous roentgen-raying was started was made up of the women attending the pre-natal clinics of the Health Department. In order to make a short study of the merit of roentgen-raying all of the group as compared with tuberculin testing and roentgen-raying only the reactors, the first 1,425 women were all tuberculin tested and a fluorograph of 4×5 inch size made.⁵ The tuberculin test was a single intradermal test using 1-1000 O.T., the so-called middle strength often used as a single dose tuberculin screen. Of these women 144 failed to return for a reading of the test and it is interesting to note that among these there were two active cases, one moderately advanced and one far advanced, found by roentgen-ray since these had all been rayed. Of those returning to have the test read 610, or 47.6 per cent, were positive. Among the positives were three active cases. Among the 671 negatives to the single dose were two active cases, later found to be positive to stronger dosage. This is a small number from which to draw conclusions and yet this study suggests the possibility of missed cases from failure to return for reading of the test and failure to respond to a single dose of tuberculin, all of which may be obviated by one visit for a fluorograph of the chest.

Since October 1939, 4,727 prospective mothers have been fluorographed and 29 active cases found, an incidence of 6.1 per 1000 examined. Of these cases five were active primary cases, eleven minimal pulmonary, eight moderately advanced, three far advanced and two pleurisy with effusion.

This is a useful survey since it affords a chance for prompt treatment for the expectant mother and also safeguards the expected child against early infection through knowledge of the mother's state at birth.

A smaller group of the population surveyed has been a group of women working under W P A as housekeepers in poor families. This has been a comparatively healthy group—among 751 women only 4 cases, or 5.3 per 1000, were found. One was minimal pulmonary, two moderately advanced, and one far advanced.

A study of the City of Detroit each year for the prevalence of tuberculosis cases reported by census areas and tuberculosis mortality rates by these areas has been quite revealing in showing wide variation in the amount of tuberculosis apparently present in various parts of the city. For instance, in 1939 when planning where extensive roentgen-ray service might be provided in a population showing the most severe experience with tuberculosis one area with over 200,000 population had a mortality rate from tuberculosis of 126 per 100,000 per year in comparison with a nearby area of slightly greater population but living under much better conditions with less congestion where the mortality rate was only 19 per 100,000.

A second fluorographic unit therefore was placed in the midst of this high mortality area in the summer of 1940 for the purpose of getting as many people as possible to come in for examination. Although it has not been possible to do any extensive house to house visiting in this area to encourage people to be examined and only voluntary efforts have been relied on, 9,326 persons have come in for examination up to March 1 of this year. Of the 8,322 of these in which the results have been checked for previously reported cases and other duplications, 121 cases have been found, or 14.5 per 1000 examined, which is definitely more than the number found in other groups. This population was 94 per cent negro. Of the 121 cases found, 22 were active primary tuberculosis, 29 minimal pulmonary, 30 moderately advanced pulmonary, 25 far advanced, 3 miliary and 12 pleurisy with effusion.

A group of young persons selected for N Y A service has recently been examined and though the group is small, 1,420, the results indicate that this age group of working young men and women have a significant amount of tuberculosis since 9 cases have been found, or 6.3 per 1000. Four of these were minimal, two moderately advanced and three far advanced.

The following table summarizes the results in each of these four groups surveyed so far.

TABLE OF CASES FOUND BY GROUPS

Group	Total Examined	Prim Act.	Min	Mod Adv	Far Adv	Miliary	Cases Found with Pleur Eff	Total Cases	Incidence per 1000
Brewster Project	8,322	22	29	30	25	3	12	121	14.5
Pre-Natal Mothers	4,727	5	11	8	3	0	2	29	6.1
Housekeepers	751	0	1	2	1	0	0	4	5.3
N Y A	1,420	0	4	2	3	0	0	9	6.3
	15,220	27	45	42	32	3	14	163	10.7

SUMMARY

The 4×5 inch fluorograph has proved useful and practical in tuberculosis case finding. Application to several different groups has demonstrated that there are significant numbers of persons with tuberculosis to be found.

From a comparison of this method with other methods of roentgen-ray examination it is believed first, that while the full sized film is the most accurate method, still it is too expensive for survey use, second, the sensitized paper is good but is still too expensive (about one-half the cost of celluloid film) and in addition is bulky to handle and store, third, the fluoroscope is not nearly as accurate as film methods and there is no permanent record (the error in fluoroscopy according to Fellows⁶ is 13 per cent when compared with large films); fourth, the miniature 35 mm film, used most extensively by De Abreu⁷ of Brazil and now being used by a number of persons in this country, it is believed sacrifices too much in accuracy in favor of economy. These very small films must be enlarged before they can be interpreted. Recently a stereoscopic technic for these very small films has been developed which improves them a great deal but still leaves much to be desired in detail.

CONCLUSIONS

The authors feel justified after this experience with the 4×5 inch fluorograph in concluding that.

- 1 It is a reasonably accurate method of making a roentgen-ray examination of the chest
- 2 Applied directly to a group without previous tuberculin screening the fluorograph has definite advantages
- 3 It lends itself well to group surveys
- 4 Surveys of certain groups in the community are definitely profitable through the discovery of many previously unrecognized cases
- 5 Wider application of fluorographic examinations will aid in the control of tuberculosis through better case finding

REFERENCES

- 1 EDWARDS, H. R. Tuberculosis case finding, *Am Rev Tuberc*, 1940, xli, 1-159
- 2 POTTER, H. E. Carman Lecture, June 1938
- 3 POTTER, H. E., DOUGLAS, B. H., and BIRKELO, C. C. Miniature x-ray chest film, *Radiology*, 1940, xxxiv, 283
- 4 BRIDGE, EZRA. Fluoroscopic roentgenography, *Am Rev Tuberc*, 1940, xlii, 155
- 5 DOUGLAS, B. H., and BIRKELO, C. C. Miniature x-ray film of the chest, *Am Rev Tuberc*, 1941, xliii, 106-116
- 6 FELLOWS, H. H., and ORDWAY, W. H. Fluoroscopy versus physical findings in the detection of pulmonary tuberculosis, *Trans Nat Tuberc Assoc*, 1937, p 51
- 7 DE ABREU, M., and LINDBERG, D. O. N. Process and apparatus for roentgen photography, *Am Jr Roentgenol*, 1939, xli, 662

FAMILIAL ACHOLURIC JAUNDICE ASSOCIATED WITH BONE CHANGES

By ERIC L COOPER, M D , *Melbourne, Australia*

FAMILIAL acholuric jaundice, frequently called congenital hemolytic icterus, is a relatively uncommon disease. In a city of approximately one million inhabitants, Melbourne, Australia, there are at least three families known to be afflicted with this inherited blood dyscrasia.

The family here recorded is apparently in no way connected with any of the families previously reported from Australia and the patients present rather unusual bone and facial abnormalities.

In all, 10 individuals in three generations have been affected. Three case histories follow.

CASE REPORTS

Case 1 Myra B, a female aged 14 years, was admitted to hospital in 1921 after attacks of jaundice which had recurred since early childhood. Her father and two paternal aunts had suffered from jaundice and enlargement of the spleen.

The patient had a red blood cell count of 3,800,000 per cubic millimeter, the leukocyte count was 8,000 per cubic millimeter and the stained film of the blood appeared normal. Tests of the fragility of red cells showed that hemolysis commenced at 0.525 per cent saline and was complete at 0.40 per cent saline. (In a normal control hemolysis began at 0.42 per cent sodium chloride.) The blood Wassermann test showed no fixation of complement. The urine contained bile pigment and the blood serum contained bilirubin in amounts larger than normal. The spleen, which extended well below the left costal margin, was removed at operation. There were dense adhesions between the spleen, the abdominal wall, and the stomach. Convalescence was uneventful and in the ensuing 15 years she had had no recurrence of jaundice. Her blood fragility is now within normal limits, hemolysis commencing at 0.45 per cent sodium chloride. Three years after the above operation Myra B married and had seven pregnancies in 12 years.

Case 2 Merle A, eldest daughter of Myra B, was first seen in 1936 at the age of 11 years. She had been pale since birth and the anemia was so severe at the age of seven years that a transfusion of blood was administered. Since early infancy she had been subject to attacks of jaundice at intervals of four to five months. During these attacks of icterus the urine became very dark in color. There had been no abdominal pain. On examination, Merle A was a bright looking child of above ordinary intelligence, small for her age but with a very large head and an extremely high forehead. The skull was shaped like a box but the sutures were not depressed. The eyes had a slant Mongolian appearance and the skin of the face was thick, greasy and of a muddy yellow-white color. The conjunctiva was slightly yellow when first seen. The trunk appeared short and the chest was large in the antero-posterior diameter. The abdomen was distended. The spleen was felt to one hand's breadth below the left costal margin and moved freely with respiration. No enlargement of the liver was detected. The child walked with a slight limp and roentgen-ray examination of the right hip revealed an early Legg-Perthes deformity. Examination

of the blood showed a red cell count of 4,260,000 per cu mm, hemoglobin (Sahli) 60 per cent color index 0.7 per cent, and a leukocyte count of 12,600 per cu mm. The red cells in a film showed a definite microcytosis—there was some polychromatophilia and extreme anisocytosis and poikilocytosis. Reticulocytes were present to the extent of 24 per cent of all red cells. A fresh specimen of blood examined showed that the majority of the red cells were less bi-concave than usual and there was no rouleaux formation.

Fragility of red blood cells was abnormal, hemolysis commenced at 0.6 per cent sodium chloride and was complete at 0.45 per cent saline. In a normal control hemolysis began at 0.5 per cent saline. The blood serum was yellow, Fouchet test positive, quantitative van den Bergh 6 units, icteric index 26 (normal 4–6), blood cholesterol 210 mg per 100 cc blood, serum calcium 13.5 mg per 100 cc, plasma phosphorus 2.5 mg per 100 cc., urine contained no bile pigments.

The roentgen-ray appearances of the skull will be described in detail later. In brief, the bones of the calvarium were enormously thickened with fine lines of denser bone radiating at right angles to the inner table. There was also an appearance similar to that seen in cerebral tumors described as hammered copper markings. The skull seemed very large in size for the age of the child. The facial bones and the skeleton in general showed no other abnormality, with the exception of the Perthes' disease in the right hip.

At operation under ether anesthesia the spleen, which weighed 30 ounces, was removed without difficulty through a left paramedian incision. There were numerous small stones in the cystic duct and the gall-bladder, deeply buried in the liver, contained stones. These were not removed. Condition after operation was good but death inexplicably occurred 48 hours later. Postmortem examination revealed no obvious cause of death, the liver was small, soft, and fatty. The heart was enlarged and the cardiac muscle pale and friable. The bones of the skull were enormously thickened and the red diploë seemed to extend almost to the external surface of the bones. The red bone marrow of the femur extended throughout the length of the bone. There was no fatty marrow. The right femoral head was fragmented and flattened, a typical Legg-Perthes' osteochondritis.

On microscopic examination of the bones of the skull red bone marrow extended almost to the surface, and erosion of bone, new bone formation and fibrosis of marrow were seen in adjacent areas of the sections. The femoral bone marrow showed extreme erythropoietic activity. The spleen showed distention of pulp spaces, some fibrosis and endothelial activity.

Case 3 Robert A., male, aged 10 years, was seen in 1936. His skin had been yellow since birth and there had been recurrent attacks of intense jaundice. There were frequent attacks of colicky pain in the right upper abdomen. His mother stated that the child's head had always been large and box-shaped, and he had complained of frequent headaches.

On examination the boy had a Mongoloid face with definite exophthalmos. The skin was thick and muddy yellow in color. The spleen was palpable to the level of the umbilicus. The liver edge was palpable but there was no tenderness over the gall-bladder area. Examination of the blood showed red cells 4,000,000 per cu mm, hemoglobin 60 per cent (Sahli) and white cells 15,600 per cu mm. The film showed definite microcytosis. A few normoblasts were seen and 20 per cent of the red cells were reticulocytes. The red cells began to hemolyse at 0.6 per cent sodium chloride and hemolysis was complete at 0.45 per cent saline. The blood serum was yellow, the van den Bergh test showed a positive delayed direct reaction and the Fouchet test was positive. Roentgen-ray examination of the skull revealed thickening of the bones of the vault with vertical radiations like "hair growing from the inner table." The suture lines were obliterated (abnormally early for a child of ten). There was

no abnormality in the remainder of the skeleton. There was some chronic bronchitis and general cardiac enlargement.

A third child, Alan A., aged 8 years, brother of these two cases was also examined and he showed no abnormality in blood or skeleton.

Another brother had died at the age of seven years with acute nephritis—the mother stated that this child at the time of death was jaundiced and had a large spleen.

Twin girls had died at the age of three months from severe anemia and jaundice.

To summarize, the mother and two children suffered from acholuric jaundice, one child is normal and three children have died with what is presumed to be anemia, jaundice and splenomegaly.

BONE CHANGES

In descriptions of autopsies of acholuric jaundice there is frequent mention of red bone marrow replacing fatty bone marrow in the long bones. Even in adult cases the whole medullary cavity of the femur is occupied by erythropoietic tissue. Many observers have recorded extra-medullary hemopoiesis in acholuric jaundice. Dawson, 1931,¹ reported masses resembling bone marrow in the hilum of the kidney and in the costo-vertebral region in the thorax. Brannan, 1927,² recorded a similar case and also a patient with bone marrow in the broad ligament. Gleane, 1936,³ reported large para-vertebral masses of bone marrow 7 centimeters in length, these were not eroding the bone but apparently were extensions from the ribs or vertebrae into the loose connective tissues of the thorax.

Hyperplasia of red bone marrow as described above is usually confined within the marrow cavity. When, however, the hyperplasia begins in early infancy, before dense cortical bone limits extension of the marrow cavity, the shape of the bone may be determined to some extent by the bulk of the bone marrow. In chronic hemolytic jaundice, the call on bone marrow is continuous, the amount of marrow increases progressively and enlargement of the bone follows.

Even in early childhood the shape of the majority of the bones is already determined by a fairly dense cortex. But in the bones of the cranial vault the outer table does not form until later childhood. In the examination of 100 roentgen-ray films of children between the ages of one and twelve years the time of appearance of a definite outer table to the frontal and parietal bones was noted (personal observation). The actual year of appearance varies but it is rare for the outer table to be seen as a definite layer of compact bone before the age of six years. The bones of the cranial vault develop in membrane and the development of bone and bone marrow goes on side by side. Normally the growth of bone exceeds that of marrow until finally the marrow is confined to the diploe. A dense cortex forms on the external surface and thus arises an outer table similar to the inner table.

which has appeared earlier in infancy. The progressive growth of bone marrow in the membranous bones of the cranial vault in acholuric jaundice leads to an enormous increase in the thickness of the diploe—furthermore, the diploe extends to the outer surface of the bone and the bony trabeculae of the diploe appear as relatively regular lines of bone formation arranged at right angles to the surface of the inner table of the bone. This radial ar-

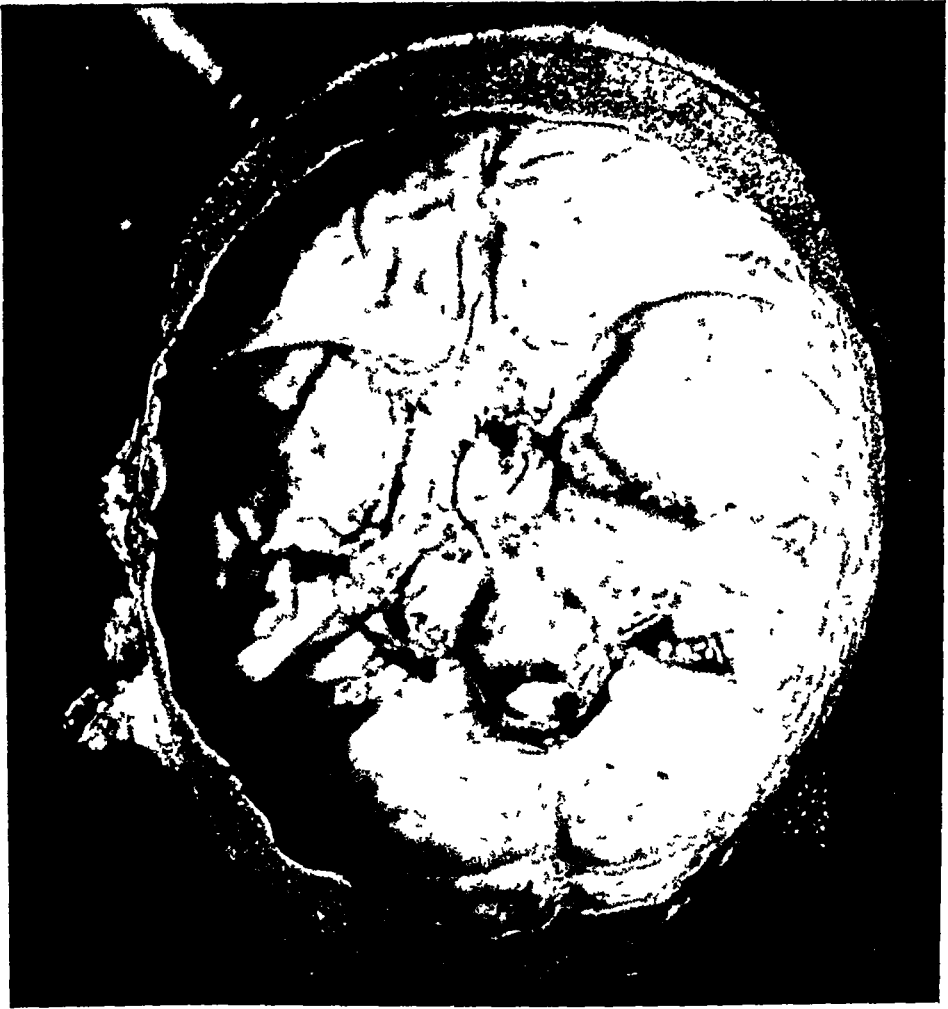


FIG 1 Base of skull of M. A., showing enormous thickness of frontal and occipital bones

angement of bony trabeculae follows the deposition of bone by the mesenchymal cells of the membrane which is giving rise to the parietal and frontal bones. Hyperplastic red bone marrow largely replaces the osteoblastic tissues and the greater proportion of the thickness of the skull consists of masses of marrow separated by fine strands of bone.

Ground sections of the parietal bone show well the contrast between the deeper layers of the diploe and the newly formed superficial bone, and roentgen-ray photographs of these sections of bone show well the radial ap-

pearance of the superficial layers of bone. During life roentgen-ray films of the skull show a similar appearance which has been well described by Sear, 1928,¹² as like "hairs growing from the inner table."

Microscopically the bone of these vertical trabeculae shows irregular laminations and irregular ossification in the fibrous tissues. Active erythropoietic marrow tissue is everywhere in close contact with the bony trabeculae.

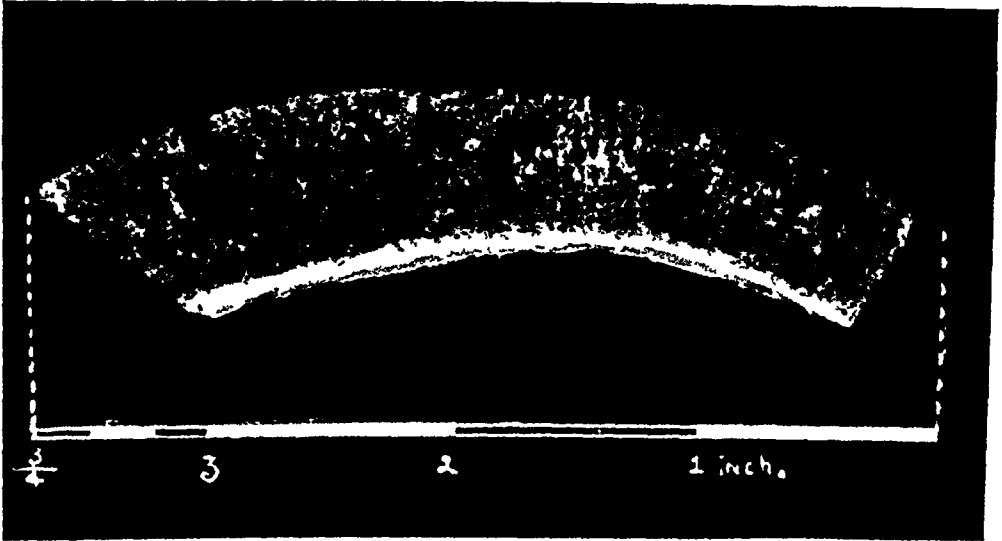


FIG 2 Ground section of frontal bone of M. A., showing dense internal bone and porous bone throughout the remainder of the thickness.

There is a complete absence of any fat cells in the bone. In some areas the marrow shows degenerative changes and is partly replaced by dense scar tissue.

The evidence points to two distinct processes going on side by side in the bone. On the one hand there is active hyperplasia of bone marrow and formation of new bone; on the other there is an exhaustion of the overstimulated marrow and replacement of the degenerating cells by fibrous tissue.

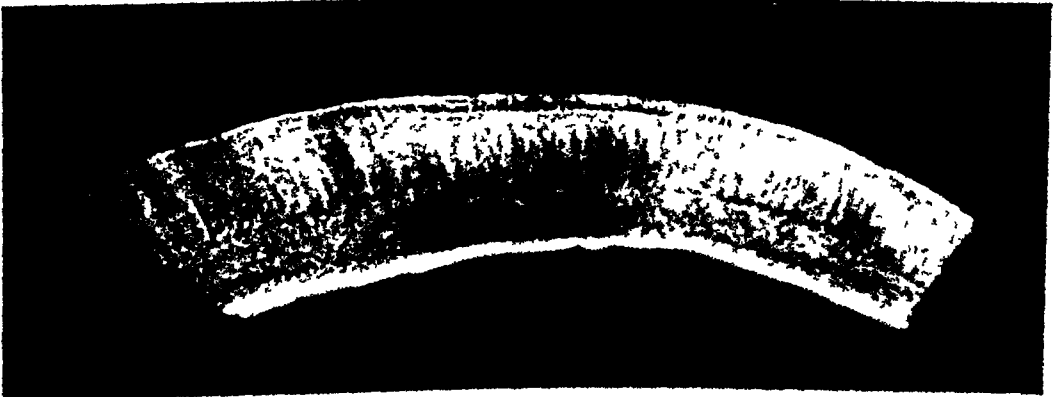


FIG 3 Roentgen-ray appearance of ground section of bone 0.5 mm. thick, showing dense internal laminae, next to this, the ordinary diploë and external as well as new bone laid down in vertical columns.

These changes have been described in some detail in the above case of acholuric jaundice. Exactly similar appearances are seen in Cooley's erythroblastic Mediterranean anemia (Mandeville, 1930⁴) and in sickle cell anemia of the negroid races (Grinnan, 1935,⁵ Le Wald, 1932⁶). In these three conditions there is an extreme hyperplasia of bone marrow beginning in early childhood and resulting in the formation of red cells which are abnormal in type. These cells are destroyed more rapidly than normal red



FIG 4 Roentgen-ray of skull of M. A., showing thickened bones of skull-cap with vertical radiating lines ("hair growing through the outer table")

blood cells and thus there is a constant stimulus to marrow activity shown by the extreme reticulocytosis common to these three diseases (Whipple, Reeves and Cobb, 1928⁷).

Many other anemias are associated with active erythropoiesis but very few anemias arise so early in life. All three of the blood dyscrasias discussed (acholuric jaundice, sickle cell anemia, and erythroblastic anemia) may arise in utero or in early infancy (Cooley, 1928⁸). The stimulus to bone marrow begins before the outer tables of the membranous bones of the skull form. The result is an appearance characteristic of these three diseases.

This vertical striation is in some respects merely an exaggeration of a condition frequently seen in roentgen-ray films of the skull in childhood. It may be that anemias other than the congenital blood dyscrasias produce a mild grade of bone change, for the appearance of vertical striation is seen in the bones of the skull of apparently normal children.

Williams, 1929,⁹ has reported similar changes in ancient skulls found in tombs in Peru, New Mexico and Arizona. Was familial acholuric jaundice,



FIG. 5 Skull-cap of M A, showing thickened bones of vault

sickle cell anemia or erythroblastic anemia common in the families of the original inhabitants of central America, or is there some other explanation of these thickened skulls?

The relative rarity of bone changes in acholuric jaundice is remarkable in view of the large numbers of cases recorded.

Gannslen, 1936,¹⁰ mentions changes in the bones and many of the American workers record the thick skulls described in this paper (Friedman, 1928¹¹). Sear, Wade, and Stigstad¹² reported one case in Sydney exactly similar to the family recorded in this paper. No connection can be traced

between the Sydney and Melbourne families. Bone changes have not been found in the Hazel family reviewed by Cowen.¹⁰

On the contrary these bone changes are relatively common in sickle cell anemia (Feingold and Case, 1933,¹² and Rose, 1929¹¹), and in erythroblastic anemia (Vogt and Diamond, 1929¹³). Although the majority of cases of

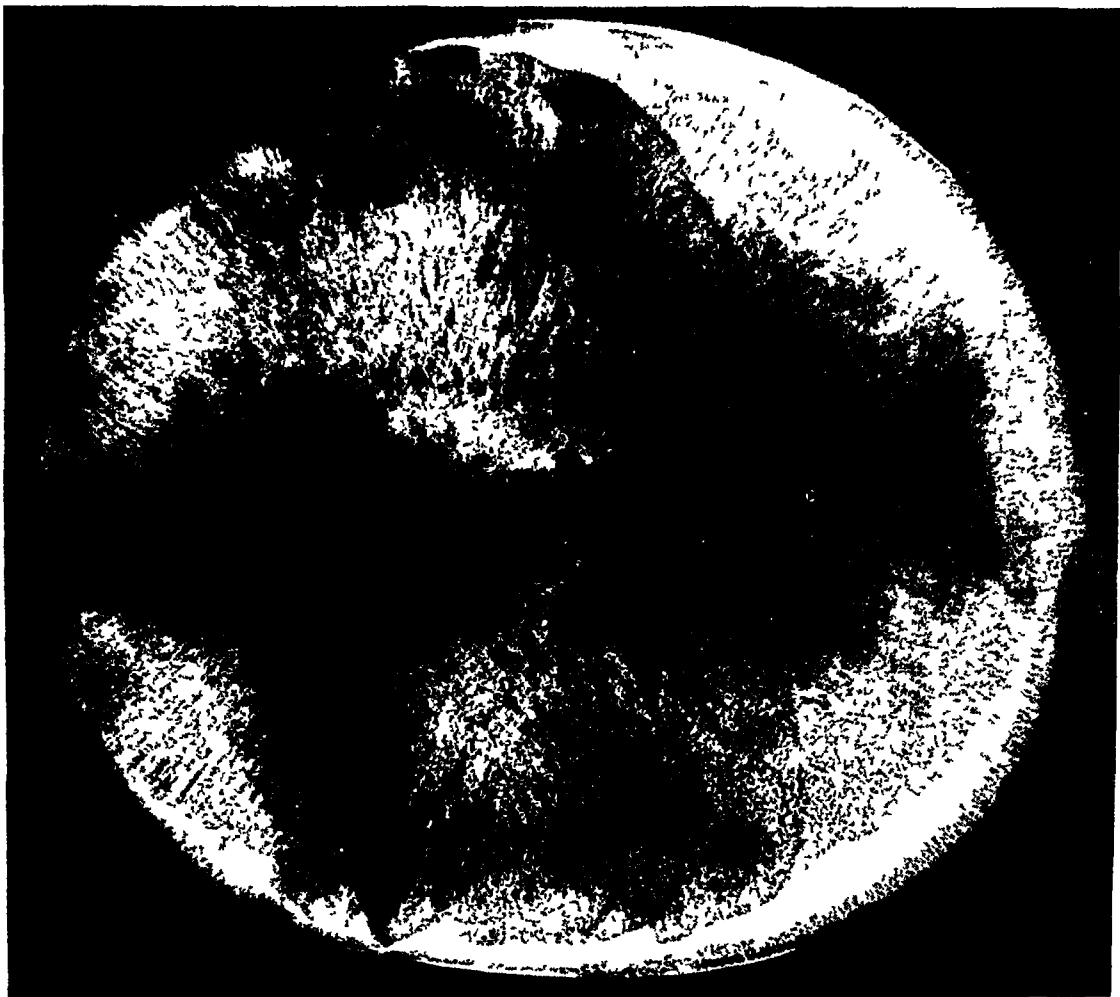


FIG 6 Roentgen-ray of skull-cap of M A, showing radiating lines of new bone formation

acholuric jaundice are chronic in type, the stimulation of the bone marrow is more severe in the other two anemias and bone changes would be expected more frequently.

An alternative explanation is that the bone changes are an associated inherited anomaly. Some families and some races may transmit skeletal defects which render the bones of the skull more susceptible to the effects of severe anemia.

SIMILARITIES BETWEEN SOME OF THE ANEMIAS

In hyperchromic macrocytic anemia the bone marrow discharges macrocytes owing to absence of the hemopoietic principle. These macrocytes are destroyed more easily than normal red cells resulting in an elevation of the blood bilirubin. The clinical picture of the lemon yellow skin of pernicious anemia is well known. Some patients with macrocytic anemia of the Addisonian type show a large amount of hemolysis. Reticulocytes are present in the blood stream to the extent of 5 per cent of the red cells, and the spleen may be greatly enlarged. In sickle cell anemia, described by Herrick and occurring as a familial disease in members of the negroid races, there is a defect in the structure of the red cells, and although the erythrocytes appear normal in the circulating blood, they assume a meniscoid or sickle shape some time after removal from the body. Meniscocyte formation is accelerated by exposure to carbon dioxide. The red cells are abnormal in other respects and are destroyed in large numbers in the enlarged spleen. A high blood reticulocyte count is usual and the bilirubin in the blood is markedly increased. In the erythroblastic anemia described by Cooley, 1927,¹⁶ in people originally coming from the countries bordering on the Mediterranean Sea there is an abnormality of red cell formation resulting in the escape of enormous numbers of nucleated red blood cells from the red bone marrow. These erythroblasts are destroyed rapidly resulting in reticulocytosis, splenomegaly and a high percentage of bilirubin in the blood serum (Baty, Blackfan, and Diamond, 1932¹⁷).

In familial acholuric jaundice the red cells discharged from the bone marrow are less resistant to hypotonic sodium chloride solutions than normal cells. The red cell is also thicker than normal and the name spherocyte has been given to this abnormal cell. These cells are destroyed in large numbers resulting in splenomegaly, reticulocytosis and bilirubinemia.

Thus in all these anemias abnormal red cells are destroyed by the normal mechanism. In macrocytic hyperchromic anemia of the Addisonian type the abnormality of the red cells can be corrected by the administration of the hematinic principle contained in liver. The other three dyscrasias at present are not susceptible to treatment by replacement therapy.

Acholuric jaundice is relieved by splenectomy but in the majority of patients the fragility of the red blood cells is unaffected. Sickle cell anemia and erythroblastic anemias are as yet not influenced by medical or surgical treatment. Chronic ulcers in the leg are common in patients with acholuric jaundice; these ulcers heal after splenectomy is performed. Similar ulcers occur in Cooley's anemia and sickle cell anemia (Graham, 1924¹⁸).

Cooley's erythroblastic anemia and familial acholuric jaundice are both associated with a peculiar change in facial appearance. This is described by Cooley as Mongoloid and includes prominent eyes with puffy eyelids—high malar eminences and nose short with depressed bridge. The skin is a muddy

yellow color and feels thicker than normal. The head is large and irregularly shaped with prominent frontal and parietal bones. The Mongoloid appearance of the face is commoner in Cooley's erythroblastic anemia.

The members of the family recorded in this paper show a similar facies associated with bone changes in the vault of the skull but with normal facial bones.

These changes in the soft tissues cannot be related directly to either the blood abnormality or the changes in the skull bones. The Mongoloid face can be described only as an associated anomaly inherited with the blood dyscrasia. This does not explain the frequency of the Mongoloid face in Cooley's anemia, the rarity in acholuric jaundice and its absence from the records of patients with sickle cell anemia.

In summary

(1) A new family is recorded of familial acholuric jaundice or hemolytic splenomegaly of Chauffard-Minkowski type.

(2) This family shows the Mongoloid facies described by Cooley in erythroblastic anemia and also the changes in the bones of the skull reported in sickle cell anemia and erythroblastic anemia.

(3) A description of the bone changes is given and an explanation of the localization to the skull is attempted.

(4) The relationships of the three related red cell dyscrasias—acholuric jaundice, sickle cell anemia and erythroblastic anemias—are discussed.

REFERENCES

- 1 DAWSON, B. E. Hume lectures on haemolytic icterus, *Brit. Med. J.*, 1931, *i*, 963-966.
- 2 BRANNAN, D. Extramedullary hematopoiesis in anemias, *Bull. Johns Hopkins Hosp.*, 1927, *xi*, 104-136.
- 3 GLEANE, H. H. *Jr. Path. and Bact.*, 1936, *xlii*, 538.
- 4 MANDEVILLE, F. B. Roentgen-ray findings in erythroblastic anemia, *Radiology*, 1930, *xv*, 72-84.
- 5 GRINNAN, A. G. Roentgenologic bone changes in sickle cell and erythroblastic anemia, *Am. J. Roentgenol.*, 1935, *xxxiv*, 297-309.
- 6 LE WALD, L. T. Roentgen evidence of osseous manifestations in sickle cell (drepanocytic) anemia and in Mediterranean (erythroblastic) anemia, *Radiology*, 1932, *xviii*, 792-798.
- 7 WHIPPLE, A. O., REEVES, R. J., and COBB, C. C. Atypical haemolytic anemia with splenomegaly in children, *Ann. Surg.*, 1928, *lxxxviii*, 380-387.
- 8 COOLEY, T. B. Likenesses and contrasts in hemolytic anemias of childhood, *Am. J. Dis. Child.*, 1928, *xxxvi*, 1256-1262.
- 9 WILLIAMS, H. U. Human paleopathology, with some original observations on symmetrical osteoporosis of skull, *Arch. Path.*, 1929, *vii*, 839-902.
- 10 GANNSEN, M. *Klin. Fortbild.*, 1936, *iv*, 607.
- 11 FRIEDMAN, L. J. Osseous changes in hemolytic icterus, *Am. J. Roentgenol.*, 1928, *xv*, 440-444.
- 12 WADE, R. B., and STEIGRAD, J. Splenomegalic jaundice with associated changes in skull, *Med. J. Australia*, 1928, *ii*, 530-532.

- 13 FEINGOLD, B F, and CASE, J T Roentgenologic skull changes in the anemias of childhood Report of a case A few notes on similar findings among the skulls of Peruvian Indians, *Am Jr Roentgenol*, 1933, xxix, 194-202
- 14 ROSE, C B Some unusual x-ray findings in skulls, *Radiology*, 1929, xiii, 508-514
- 15 VOGT, E C, and DIAMOND, L K. Congenital anemias, roentgenologically considered, *Am Jr Roentgenol*, 1930, xxiii, 625-630
- 16 COOLEY, T B, WITWER, E R, and LEE, P Anemia in children with splenomegaly and peculiar changes in bones, report of cases, *Am Jr Dis Child*, 1927, xxxiv, 347-363
17. BATY, J M, BLACKFAN, K D, and DIAMOND, L K Blood studies in infants and in children, erythroblastic anemia, clinical and pathologic study, *Am Jr Dis Child*, 1932, xliii, 667-704
- 18 GRAHAM, G S A case of sickle cell anemia with necropsy, *Arch Int Med*, 1924, xxxiv, 778-800
- 19 COWEN, S O Familial haemolytic splenomegaly, *Med Jr Australia*, 1922, ii, 545-561.

NEUROLOGICAL, MEDICAL AND BIOCHEMICAL SIGNS AND SYMPTOMS INDICATING CHRONIC INDUSTRIAL CARBON DISULPHIDE ABSORPTION ¹

By F H LEWY, M D , *Philadelphia, Pennsylvania*

ACCORDING to the statistics of the Textile Economics Bureau, 78,000,000 pounds of carbon disulphide (CS_2) were employed in 1937 in the 19 viscose rayon plants operating in the United States of America. Thousands of workers were thus exposed to the potential danger of absorbing CS_2 fumes and falling victim to intoxication. Despite this fact five short case histories published before 1905 (Bard,¹ Peterson,² Heath,³ Jump and Cruice,⁴ Francine,⁵ and one report of recent years (Goidy and Trumper⁶)) constitute all that American medicine has contributed to this subject.

Credit should be given to Dr. Alice Hamilton for 15 years of relentless and eventually successful crusade against the danger of CS_2 intoxication in viscose rayon plants. Dr. Hamilton had listed this risk as early as 1925.⁷ In 1937⁸ she raised again her warning voice to point out that "the lack of interest in the pathological signs and symptoms accompanying and following industrial CS_2 poisoning was in inverse proportion to its medical and sociological importance in this country which is the second largest producer of rayon in the world." Finally, in 1938, Dr. Hamilton found a propitious constellation in the Commonwealth of Pennsylvania enabling her to induce the Department of Labor and Industry to conduct—with the energetic assistance of Miss Lillian Erskine, then Consulting Expert of the Department—a "Survey of Carbon Disulphide and Hydrogen Sulphide Hazards in the Viscose Rayon Industry."⁹ †

Requested to act as Consultant to the State in this investigation I had the good fortune to secure the cooperation of the various departments of the University of Pennsylvania Medical School. Thus, 120 workers were examined by a neurologist, psychiatrist, ophthalmologist, otologist, internist and hematologist. Finally, a number of biochemical studies were made (Hamilton and Lewy¹⁰).

The scientific gains of these examinations are reported in this and in the papers of Dr. F. J. Braceland^{11a} and Dr. B. J. Alpers and myself,^{11b} as well as in a previous paper of Dr. R. McDonald.¹² The beneficial practical result of the cooperative investigation was that the rayon industry in this State became deeply concerned with the problem. It availed itself of experts in the

* Received for publication February 3, 1941.

From the Neurosurgical Department in the Hospital of the University of Pennsylvania.

This investigation was conducted under the auspices of the Department of Labor and Industry in the Commonwealth of Pennsylvania.

† See here for the complete literature of the subject.

field of Industrial Hygiene and is going to reduce the inherent risk of the manufacturing process to a minimum with the help of adequate control of ventilation and automatic machinery

This paper does not deal with acute CS_2 intoxications but with the consequence of exposure to CS_2 fumes over a long period of life. We prefer to use the term " CS_2 absorption" in reporting the findings in these individuals because all of them, with three exceptions, were actually working at the time of the examination and did not consider themselves ill, although they admitted various complaints when specifically questioned

GROUPING OF PATIENTS AND HISTORIES

For the sake of expediency, each of the 120 viscose rayon workers examined was graded according to the severity of signs and symptoms in a conference of six medical specialists from the University of Pennsylvania Hospital cooperating in this investigation. It is obvious that such a grading will always be more or less arbitrary, although certain numerical principles were applied as a basis for judgment. The general appearance and condition of the individual, however, could not be neglected. As a whole, it was surprising to notice in how few instances there was any dissension among the six specialists concerning the severity of a case.

In the following, the history of representatives of two of the four groups, namely: mild (I), moderately severe (II), severe (III), and very severe (IV) cases, is given as an example.

Group I, comprising almost 40 per cent of the examined, represents the largest group.

L. C., aged 42, of English descent, had worked for over 13 years in the spinning department of a viscose rayon plant. He was married, had one child, and lived in moderate circumstances. He had never been severely ill, did not use any medicine, and had not spent any money for personal medicine during the preceding few years. About six or seven years previously, i. e., at the age of 35 or 36, he began to lose both libido and sexual power. Later he noticed shortness of breath and nausea before meals although his appetite remained fair. During the preceding two years he had begun to suffer from frontal and occipital headaches and from dizziness when stooping over. Sleep became poor. His hands got numb while asleep, and he had to rub his arms when he awakened. At times he had the sensation of pins and needles in his arms. His calves sometimes ached so badly that he had to prop up his feet to get relief.

The following pathological signs were observed:

P. E. Slurring of the ventricular complex in electrocardiogram, liver slightly enlarged; bleeding of gums; and ecchymoses.

N. I. Pupillary reflexes to light slightly decreased (72 per cent)*, corneal reflexes markedly decreased (0.68 mg/mm²)†, marked dip in the audiometer curve at 4,096 frequencies, slight nystagmus on right and left gazes, Troemner sign of the

* The pupillary reflex was measured with the Hess-Zeiss pupilloscope. See ABRAHAM, F. H.: *Clinical physiology of the eye*, 1933. The MacMillan Company, New York, p. 63.

† The corneal reflex was measured with graded jets of air. For normal values see table 3.

right hand, hyperactive patellar and Achilles reflexes. When the arms were extended and the eyes closed, the left arm sank. Pastpointing downward with the left arm, tenderness to pressure over both radial nerves, mild electrical underexcitability of the ulnar nerves ($7.3V\mu C$)*

Diagnosis Mild polyneuropathy, possibly with involvement of the central nervous system

Going over this history, one might be impressed by the variety and comparative gravity of symptoms. However, the man himself was so little impressed by them that he did not even consider consulting his physician. A hardy individual, he was not concerned by minor inconveniences which, in his opinion, were too slight to worry about.

There were only three pathological signs which occurred frequently in this group. About one-third of the 47 persons in Group I showed a decrease of the pupillary and corneal reflexes, and about one-half showed a pathological electrical irritability in the peripheral nerve-muscle apparatus. Nystagmus was observed in 17 per cent of them, the remainder of the signs were present in less than 10 per cent (table 3).

Not one of these signs alone gives conclusive evidence of CS_2 absorption, but their combination should always arouse the curiosity of the family doctor, or the consultant, as to the occupation of his patient.

Group II comprises almost 30 per cent of all examined.

The main difference between Groups I and II lies in the increasing frequency with which the various neurological signs appear in Group II. Indeed, some of them, such as nystagmus and tremor, reach their greatest incidence in Group II, while in most of the columns the percentage of pathological signs rises considerably (table 3). As a matter of fact, the gap in the frequency of pathological signs between Groups I and II is greater in all columns than between II and III, and often greater than between II and IV. No increase in frequency from Group I to Group II is visible in the charts recording the electrical over- or underexcitability of the peripheral nerves. However, the frequency with which specific pathological signs appear in each of the four groups is only one standard of severity. We shall see later that, at least in some syndromes, the severity of the phenomena themselves plays a preëminent rôle in the final grading of the individual.

Group III consists of 22 workers, or 18.3 per cent of all examined.

P. D., aged 54, was married and the father of six living children. He had worked in the churn room of a viscose rayon plant for almost 19 years. He had suffered from headaches for many years but was not so greatly troubled at the time. He was easily fatigued, restless and sleepless, stated that he jerked in his sleep, and complained of vertigo. He was constipated and took a laxative twice a week, his appetite was poor and he was often nauseated. His arms and legs were numb. At times the right arm felt as though it were stiff and paralyzed. His legs felt heavy and he had great difficulty in ascending stairs. He trembled upon the slightest exertion or excitement.

* Microcoulomb is the product of voltage times microfarad or time in milliseconds. For technical reasons the actual figures are given as the square root of microcoulombs ($V\mu C$). The normal values for the various muscle groups are given in table 4.

Other strains, like those of Birkhaug (erysipelas) (three of four strains), also produced a toxic factor, but in no appreciable quantities until six or seven days had elapsed. All of the organisms produced toxin, some earlier than the others.

Two toxins were made up in large batches—No. 420 (Crook's strain from puerperal infection) and No. 624 (Frost's strain from septic sore throat). We attempted to standardize the toxin by skin test dosage in the same fashion as the Dicks standardized their material. The technical accuracy of our standardization procedure was not completely satisfactory in that our standard solutions were probably understandardized as compared with the Dick material. However, the results were suggestive and in the right direction.

Fifteen volunteer susceptibles were injected with five doses of the combined material, seven were still positive to the Dick test and eight had become negative within one month after the last injection. Seven of these individuals contracted scarlet fever, one of the seven might have had a rash due to the toxin injection, since it occurred 24 hours after the fifth injection (table 8).

That we had immunized some positive susceptibles to a degree, at least, is seen from the fact that on admission to the hospital four of the seven patients who contracted scarlet fever were negative not only to one, but to two and three skin test doses of Dick toxin, three were still positive on admission. No definite conclusions can be drawn from this work. It only suggests the fact that probably all streptococci produce toxins.

ORAL VACCINATION

Because of the reactions following the use of naked scarlet fever toxin, some experimentation has been done by the Dicks^{21, 22} on oral vaccination. An average of 75 million skin test doses of toxin was recommended as the immunizing dose, starting with 100,000 and increasing to 6 to 10 million skin test doses a day for the last three to six days. Of 17 individuals in one group, 11 were immunized. In another group of 102 persons, 98, or 94.7 per cent, were immunized.

This method of vaccination is in the experimental stage. If it proves satisfactory, the objection to scarlet fever immunization on a wholesale measure will be materially lessened.

COMMENT

The recent Army Bulletin No. 81²³ recommends that active immunization should be given to nurses with positive reactions to Dick tests and for orderlies assigned to care for patients with scarlet fever. It was not recommended for general use to the Surgeon General because there is a "high percentage of immune subjects among adults, and because at least 5 or more injections are usually required to produce immunity."

Susceptible young adults in contagious disease hospitals contract the disease because of massive exposure, etc., and it has been proved repeatedly that these individuals can be protected. It is equally obvious that where there is crowding and disease occurs, as in the army, cross infections will follow. It is not clear why susceptible exposees in the army should not be immunized.

In pediatric practice, the only reason the vaccine may not be used is because of the reactions, but physicians, especially pediatricians, can easily immunize their patients, especially if they appreciate the reactions and avoid them by injecting a greater number of smaller doses.

CONCLUSIONS

1 Susceptible adults are easily immunized with scarlet fever toxin to the point where they will have a negative Dick reaction.

2 Eight nurses successfully immunized to a negative Dick test developed scarlet fever, an attack rate of 0.6 per cent.

3 Active immunization against scarlet fever has become a standard procedure in most hospitals for contagious diseases.

4 Active immunization, though not a public health measure as yet, can be used by private physicians in their practice, provided they take precautions to avoid complications.

BIBLIOGRAPHY

- 1 POPE, ALTON S. Studies on the epidemiology of scarlet fever, *Am Jr Hyg*, 1926, vi, 389.
- 2 HEKTOEN, LUDWIG and JOHNSON, CHARLOTTE. Prevention of diphtheria and scarlet fever in nurses, *Jr Am Med Assoc*, 1934, cli, 41.
- 3 PLACE, EDWIN H. Result of active immunization of nurses against scarlet fever, *Am Jr Pub Health*, 1938, xxviii, 137.
- 4 BENSON, W. T., and RANKIN, A. L. K. Active immunization against scarlet fever, *Lancet*, 1934, ii, 1357.
- 5 ANDERSON, GAYLORD W., and REINHARDT, WARREN I. Scarlet fever immunization of nurses, *Jr Infect Dis*, 1935, lvii, 136.
- 6 DICK, GEORGE F., and DICK, GLADYS, H. Scarlet fever, First Edition, 1938, Year Book Publishers.
- 7 RAPPAPORT, BENJAMIN. Active immunization to scarlet fever with less reactions, *Jr Am Med Assoc*, 1936, cvi, 1076.
- 8 ANDERSON, GAYLORD. Scarlet fever immunization with formalized toxin, *Am Jr Pub Health*, 1938, xxviii, 123.
- 9 TOYODA, T., MORIWAKI, J., FUTAGI, Y., and OKAMOTO, M. Value of immunization against scarlet fever with streptococcus toxins, *Jr Infect Dis*, 1930, xli, 219.
- 10 HENRY, J. NORMAN. A study of active immunization against scarlet fever, *Jr Am Med Assoc*, 1935, cv, 488.
- 11 KNIGHTS, EDWIN M. Immunization to scarlet fever of Providence City Hospital student nurses, *Jr Lab and Clin Med*, 1929, xiv, 614.
- 12 PLATOU, E. S. Scarlet fever prevention by immunization, *Jr Pediat*, 1934, v, 531.
- 13 HEALEY, C. E. Cause of joint pains occurring during active immunization with scarlet fever streptococcus toxin, *Jr Am Med Assoc*, 1937, cviii, 628.
- 14 BOOTHBY, V. M., and UNDERWOOD, M. T. Scarlet fever cross infections in a contagious disease hospital. (In preparation.)

- 15 LARSON, W P, HUENKENS, E J, and COLBY, WOODARD Immunization against scarlet fever, Jr Am Med Assoc, 1926, lxxxvi, 1000
- 16 VELDEF, M V Purification and precipitation of the erythrogenic fractions of scarlet fever toxin and its antigenic value, Pub Health Rep, 1937, li, 819
- 17 FUTAGI, Y Improvement of the prophylactic immunization against scarlet fever by means of anatoxin after Ramon's Method, Jr Immunol, 1930, xix, 451
- 18 PARK, WILLIAM H, and SPIEGEL, ROSE GORDSCHMIDT Complexity of the scarlet fever toxin and antitoxin, Jr Immunol, 1925, x, 829
- 19 KIRKBRIDE, MARY B, and WHITTIER, MARY W Comparison of reactions in individuals to toxins prepared from three strains of scarlet fever streptococci, Proc Soc Exper Biol and Med, 1924, xxii, 85
- 20 TRASK, J D, and BLAKE, F G Heterologous scarlet fever, Jr Am Med Assoc, 1933, ci, 753
- 21 DICK, GEORGE F, and DICK, GLADYS H Toxin for oral immunization against scarlet fever, Jr Am Med Assoc, 1940, cxv, 2155
- 22 DICK, GEORGE F, and DICK, GLADYS H Antitoxic immunity resulting from administration of toxin by mouth, Jr Am Med Assoc, 1932, xcvi, 1436
- 23 Army Bulletin No 81, Jr Am Med Assoc, 1941, cxvi, 513
- 24 References quoted by Platou ^{1,2}

- a DICK, G F, and DICK, G H Am Jr Dis Child, 1929, xxviii, 905
Idem Kentucky Med Jr, 1931, xli, 172
- b RHODES, PAUL Jr Am Med Assoc, 1931, xcvi, 153
- c Idem Jr Iowa Med Soc, 1931, xxi, 443
- d KNIGHTS, E M Jr Lab and Clin Med, 1928-29, xiv, 614
- e KIEFER, G Jr Am Med Assoc, 1928, xci, 1885
- f TOWNSEND, J Boston Med and Surg Jr, 1927, cxcvi, 612
- g PARK, W H, and SCHROEDER, M Am Jr Pub Health, 1928, xviii, 1455
- h HEKTOEN, L Jr Am Med Assoc, 1934, cii, 41
- i PARK, W H Personal communication
- j PLATOU, E S Minnesota Med, 1932, xv, 697
- k PEACOCK, S, WERNER, M, and COLWELL, C Am Jr Dis Child, 1932, xli, 494
- l BLATT, M L Jr Am Med Assoc, 1932, xcvi, 1437
- m BROADBENT, J Lancet, 1932, ii, 823
- n RADOYE, T Rev d'hyg, 1930, li, 94
- o BOYNTON, R Personal communication
- p VELDEF, M V Pub Health Rep, 1933, xlviii, 549
- q HARRINGTON, F E Personal communication
- r BROKMAN, HENRY Kinderarztl Praxis, 1931, ii, 200
- s Idem Ibid
- t LICHTENSTEIN, A Acta Paediat, 1930-31, x, 543
- u PLATOU, E S Minnesota Med, 1932, xv, 697
- v Idem Ibid

THE TREATMENT OF ACUTE EMPYEMA; TREATMENT BY CONTINUOUS TIDAL IRRIGATION AND SUCTION (HART) ¹

By BEN KLOTZ, B A , M D , F A C S , *Washington, D C* , and
BERNARD LIDMAN, B S , M D , *Norfolk, Virginia*

THE method of treating acute empyema by tidal irrigation and suction, described by Hart,^{1, 2, 3, 4, 5, 6} was introduced in 1929 on the medical and surgical services of the Sinai Hospital, and since that time 33 cases have been treated by this procedure. In four of these, tidal drainage was insufficient and was followed later by rib resection and thoracotomy, they will be discussed separately later in this report. In 30 of the 33 cases, the operative procedure was performed and the subsequent course was followed personally by the senior author.

Technic The details of the method, operative and postoperative, have been clearly given by Hart,⁶ and we followed them closely. In all our cases (including those with a broncho-pleural fistula) we used the apparatus as described and illustrated in his paper in 1935.⁶ We did not follow closely enough his directions for the case of the bronchofistula in our series. As a result of our own experience we wish to make the following suggestions about the care of the apparatus which we think may be helpful.

To prevent leakage, especially in children, it proved advisable to secure the tube in the chest snugly. This was accomplished by tightening the adhesive on the front of the chest after the patient was turned on his back (the adhesive having been first applied with the patient on the sound side). Also, to prevent excess pulling on the tube by the nurse when she changed the bed linen, we allowed an increase in the length of the tubing leading to the irrigating bottle. Apparently this did not interfere with the force of the irrigation.

To prevent air from entering through the flask containing the fresh fluid, we marked the flask to indicate a point beyond which the fluid level was never allowed to fall.

Thick pus and fibrin did not give us much concern, especially if we aspirated most of the thick pus and irrigated the cavity at the time of the thoracotomy and before we attached the bottles. If plugging did occur, it was only temporary and the plug could always be dislodged without disconnecting the apparatus.

Some cases demand more attention than others. It is an advantage to have personnel familiar with the operation and care of the apparatus. We found nurses more suitable than house-officers because the former are more permanent in their positions.

The tube in the chest can be withdrawn at one time if complete suction has been maintained for about five days. The shortest length of the tube in the chest to give proper irrigation measured between $4\frac{1}{2}$ and $5\frac{1}{2}$ inches.

The chief chance of complication developed at the time of the insertion of the trocar. Preoperative roentgen-rays should always be taken in order to locate if possible the height of the diaphragm. Great care should be exercised in locating

* Received for publication August 23, 1939.

From the Departments of Surgery and Medicine, Sinai Hospital, Inc., Baltimore, Maryland.

the proper interspace and it is probably safer to go a space higher than in the reverse direction

Of the 33 patients treated, six died, i e., a mortality of 18 per cent. The mortality in the 29 patients treated by closed drainage alone was 20·7 per cent (table 1)

TABLE I
Mortality

	No. Cases	Deaths	Per cent Mortality
Tidal irrigation only	29	6	20·7
Tidal irrigation plus rib resection	4	0	0·0
Total	33	6	18·2

There were six deaths in the group of patients treated with continuous tidal irrigation and suction. In three cases, death was directly attributable to acute purulent pericarditis, associated, in one patient, with acute peritonitis. At necropsy, the empyema cavities were almost entirely clear. Two infants, aged 21 and 12 months respectively, were critically ill and almost moribund when they were admitted to the hospital. In both, tidal drainage worked well, but their toxic state could not be relieved. The sixth fatality occurred in an eight year old girl who had unilateral empyema during a fulminating pneumonia which involved all five lobes and which was complicated by acute encephalitis and hemiplegia (table 2)

TABLE II
Fatalities

Age	Organism	Patient's Condition at Operation	Time of Death—Days Postop	Cause of Death
11 yrs	Pneumococcus Type IV	Fair	36	Suppurative pericarditis
5 mos	Pneumococcus Not typed	Poor	2	Suppurative pericarditis
10 mos	Pneumococcus Not typed	Poor	3	Suppurative pericarditis peritonitis
21 mos	Pneumococcus Not typed	Moribund	1	Systemic infection
12 mos	Pneumococcus Not typed	Moribund	4	Systemic infection
8 yrs	Pneumococcus Type I	Very toxic	7	Encephalitis, hemiplegia, 5-lobed pneumonia

All the patients who died were under the age of 12, four were less than two years old (table 2). In the group under two years of age, the mortality rate was 57 per cent which is high, but it must be recalled that two of these patients died of purulent pericarditis and the other two because of an overwhelming systemic infection, furthermore, the number of patients in this

age group is very small. In all cases, the irrigation apparatus functioned satisfactorily.

The age incidence in the group (29) treated by tidal irrigation alone ranged from five months to 46 years, 22 were under the age of 16 (table 3).

TABLE III
Age Groups

Age	No. Cases	No. Deaths	Days Treatment (Average)
Birth to 6 mos	1	1	
7 mos to 12 mos	1	1	
13 mos to 24 mos	5	2	27
2 yrs to 5 yrs	6	0	39
6 yrs to 10 yrs	5	1	35
11 yrs to 15 yrs	4	1	43
16 yrs to 20 yrs	1	0	48
21 yrs to 30 yrs	3	0	46
31 yrs to 50 yrs	3	0	23
	29	6	37

The "average duration" of treatment (37 days) comprises the time interval between the institution of drainage and the final withdrawal of the tube.

Bacteriological studies show that no patient with streptococcal or staphylococcal empyema died, which is in agreement with Hart's observations.⁴ All six of the deaths occurred in patients who had pneumococcal empyema: one type I, one group IV, and four in whom the pneumococci were not typed (table 4).

TABLE IV
Organisms

Organism	Number of Cases	Number of Deaths
<i>Pneumococcus</i>		
Type I	8	1
Type II	0	0
Type III	2	0
Group IV	5	1
Not typed	10	4
<i>Staphylococcus</i>		
<i>albus</i>	1	0
<i>aureus</i>	1	0
<i>Streptococcus</i>		
<i>hemolyticus</i>	2	0

Almost all of our patients had extensive, free empyema which was drained easily. In two patients with bilateral empyema, the fluid was pocketed on one side, but there was no interference with irrigation. In two infants who died of acute suppurative pericarditis the empyema drained was encapsulated in a single large pocket, and in both necropsy demonstrated that the pleura elsewhere was clear. One 39-year-old patient, with right-sided interlobar empyema, had complete closure of the cavity in 12 days.

Twenty-three of the patients had pneumonia affecting more than one lobe. Fourteen had consolidation of two lobes, and seven had lesions involving three lobes (table 5)

TABLE V
Lobes Involved

Number of Lobes Involved	Patients	Recovered	Died
1	6	5	1
2	14	12	2
3	7	5	2
4	1	1	0
5	1	0	1

During the period that this method of treatment of acute empyema has been employed at this hospital, open drainage has also been used. The medical service has endeavored to select those cases for tidal drainage that would profit best by this procedure, and has, at the same time, advised open thoracotomy for many patients who appeared to require that operation.

In reviewing these cases, several major indications for tidal drainage become apparent and these may be summarized as follows:

	Number of Patients
Condition too poor for rib resection	4
Streptococcal empyema	2
Synpneumonic empyema	12
Bilateral empyema	3
Broncho-pleural fistula	4
Septicemia with synpneumonic empyema	4

Under tidal drainage the temperature ordinarily returned to normal within three or four days after the irrigation was begun. However, in the four cases with broncho-pleural fistula complicating pneumonia, elevations of temperature persisted from two to three weeks after drainage was instituted. In some instances slow resolution of the pneumonic process resulted in pyrexia beyond four days, in one case there was a recrudescence of the pneumonia, and in another, a dissemination of the pneumonia to the contralateral side. "Catheter fever," so-called because it is caused by a plugging of the tube by clumps of fibrin, occurred occasionally, but was readily corrected by mechanical flushing or irrigation with Dakin's solution.

Broncho-Pleural Fistula. In the treatment of broncho-pleural fistula, tidal drainage was very effective, although the results obtained in this series were not as spectacular as those reported by Hart^{2,3}. In almost all of the latter's cases, the fistula closed within 48 hours. In our series (table 5) closure was not effected until a much longer period had elapsed, probably for the reason already mentioned, when closure did take place, however, the healing was permanent. The series included four cases, without a single mortality.

Bilateral Empyema. Recovery followed tidal irrigation in three cases of bilateral empyema. In this group the results were more satisfactory than

those noted by Hart,^{2, 3, 4} and are reported in detail below. All three patients had bilateral pneumococcal empyema, one due to Type I pneumococcus and two due to infection with group IV pneumococci.

TABLE VI
Broncho-Pleural Fistulae

Patient	Age	Duration of Empyema— Days	Duration of Fistula—Days Before Irrigation	Closure Days— Postop	Irrigation Total Days
R E	18 mos	3	2	20	32
N J	2 yrs	5	5	62	71
D S	3 yrs	8	7	11	32
C K	21 yrs	8	4	12	47

In one case, N J, the pneumothorax was present before any diagnostic needling was done, in the others it was detected only after diagnostic thoracenteses.

R R, two years old, was admitted February 24, 1936, with acute otitis media. Three days later signs of pneumonia of the left lower lobe developed, followed in days by signs of empyema (March 9). Four days after the left-sided pneumonia became manifest, signs of consolidation of the right lower lobe were detected. Signs of empyema appeared seven days later (also March 9). Tidal drainage was instituted on the right side two days after the discovery of the effusion there, and fluid was found to be pocketed. The temperature fell to normal within 48 hours but rose again within a few days, and on March 20 tidal drainage was begun on the left side, where the fluid was free. Both irrigation apparatuses worked satisfactorily and were run simultaneously throughout the course of the illness. Drainage and irrigation were maintained for 52 days on the right side, for 30 days on the left side.

G P, six years old, was admitted November 23, 1929, with pneumonia of ten days' duration, involving the right middle and lower, and the left lower lobes. Fourteen days after the onset of the illness signs of bilateral empyema became evident. Tidal drainage was begun on the left side four days later, on the right side after an interval of seven days. The course was complicated by an acute pyelonephritis and by a recrudescence of the left lower lobe pneumonia, but continuous irrigation was uninterrupted. Total days of irrigation: right side—31, left side—37.

G H, seven years old, was admitted on October 30, 1933, with pneumonia involving the right upper, middle, and lower lobes, of five days' duration. Three days later, signs of empyema appeared. After three aspirations, tidal drainage was begun eight days after discovery of the empyema. Two days after the institution of continuous drainage, pneumonia of the left lower lobe developed, followed in 14 days by empyema on that side. Tidal drainage was started within 24 hours, both apparatuses functioning concurrently. The subsequent course was satisfactory. Total days of irrigation: right side—51, left side—32.

As can be seen from table 7, many of the patients included in this series developed serious complications, frequently rendering treatment of any kind difficult and prolonging the period of hospitalization. Most of the complications could not be attributed to the method of therapy, but it was evident, as noted by Hart,² that precautionary measures can minimize the occurrence of at least three untoward events. These are (1) Reformation of the cavity, because suction is removed too early, (2) pocket formation because suction is applied too rapidly, and (3) osteomyelitis of a rib.

There were four patients in whom, for various reasons, rib resection and thoracotomy were performed after preliminary tidal irrigation and suction.

One patient, an acutely ill 61 year old man with severe diabetes, was carried safely over an old interlobar empyema by tidal irrigation for two months. Because of the rigid walls, the cavity could not be reduced to less than 15 c.c. capacity. Rib resection and removal of the roof of this cavity were followed by complete recovery within a year.

TABLE VII
Complications

	Total	Recovery	Deaths (6)
Not referable to treatment			
Bilateral empyema	3	3	0
Bilateral pneumonia	11	8	3
Pericarditis	3	0	3
Peritonitis	1	0	1
Septicemia	9	9	0
Encephalitis	1	0	1
Pneumonitis media	7	4	3
Broncho-pleural fistula	4	4	0
Septic abscess	1	1	0
Osteoarthritis	1	1	0
Pyelonephritis	2	2	0
Tuberculosis	1	1	0
Myocarditis with cardiac insufficiency	3	2	1
Osteomyelitis of rib (secondary to trauma before admission)	1	1	0
Subcutaneous emphysema, infected (preoperative)	1	1	0
Referable to treatment			
Reformation of cavity, suction removed too early	1	1	0
Pocket formation, suction applied too rapidly	3	3	0
Osteomyelitis of rib	1	1	0

In a 27 year old woman, from whose pleural fluid pneumococcus Type III and *Hemophilus influenzae* were cultured, the empyema reformed because suction was removed too early. After open thoracotomy was done she convalesced uneventfully and was completely healed six months after rib resection.

There was one patient in whom tidal irrigation was unsatisfactory from the time it was instituted. This was a young man of 23, who was found, after rib resection and wide exposure of the thoracic contents, to have post-pneumonic lung abscesses (hemolytic *Staphylococcus aureus*), with multiple empyema pockets. Another patient, a 45 year old woman, developed a complication which might be considered the result of a technical error. Pus had been obtained with the aspirating needle placed supposedly in the right eighth interspace. On insertion of the trocar, however, pus was not obtained. A roentgen-ray film then showed a high diaphragm with the catheter in the ninth interspace. Failure to take a film before thoracentesis certainly contributed to this error. She developed a subphrenic abscess,

presumably as a result of the perforation of the diaphragm, but recovered completely after a rib resection for the drainage of the empyema and after another one subsequently for the drainage of the subphrenic abscess

SUMMARY AND CONCLUSIONS

During a period of nine years, 33 patients with acute empyema have been treated by closed drainage, with continuous irrigation and suction (Hart). The mortality rate in the entire series was 18 per cent; in the 29 cases treated by irrigation and suction alone (without subsequent open drainage), 20 per cent. The six deaths that occurred were due to pre- and post-operative complications, and were in no way related to the mode of treatment. No patient with streptococcal or staphylococcal empyema died.

Tidal irrigation functions equally well in the presence of thick or thin pus, provided the person responsible for the management of the apparatus is familiar with the technic of removing clumps of fibrin from the drainage tube which may become plugged in those cases in which thick pus is found.

The indications for closed drainage by the Hart method are reviewed.

Tidal irrigation and suction were found to be effective in four cases of broncho-pleural fistula and in three cases of bilateral empyema, without a death in either group.

Complications due to the method of treatment are noted, particularly in two patients in whom tidal drainage was followed by rib resection and thoracotomy.

None of the patients treated by tidal drainage alone developed chronic empyema or a persistently draining sinus*. Two adult patients developed chronic empyema following tidal irrigation supplemented by rib resection, one healing within six months, the other within one year.

The closed method of treating empyema requires the constant personal attention of the operator. If he is not willing to give this he should not employ the method. The technic and the care are simple and easily learned after several patients have been treated.

Dr. Deryl Hart set up and supervised the treatment in several of the early cases herein reported. We wish to take this opportunity to express our appreciation of his kindness.

Our thanks are gratefully extended to Dr. Charles R. Austrian for his encouragement and advice in the preparation of this report.

* One patient, F. R., was admitted first in 1935, at the age of 18 years, with a massive empyema on the left side, at that time the empyema was apparently successfully treated by tidal irrigation. She ran a smoother course than any other patient (according to notes on her chart) previously so treated. Her temperature never went over 100° F. On that admission she gave a history of rib resection for left sided empyema at three years of age.

Since this report was written she was readmitted July 12, 1938 with a draining chronic left empyema which had been operated upon at another hospital in another city. On July 20, 1938 her left chest was explored after resecting part of the seventh, eighth, and ninth ribs. Recovery was slow and she healed down to another chronic sinus. On January 5, 1939 the chronic pleurocutaneous sinus tract was excised. She was finally discharged on January 26, 1939 with wound healed, having had a normal temperature for 10 days.

BIBLIOGRAPHY

- 1 HART, DERYL Acute empyema Treatment by continuous tidal irrigation and drainage dependent on normal respiratory movements, Arch Surg, 1928, *LVII*, 102
- 2 HART, DERYL Empyema (acute, chronic and tuberculous) Report of 50 cases treated by tidal irrigation and suction, Jr Am Med Assoc, 1929, *XCII*, 1724
- 3 HART, DERYL Empyema Method of treatment by tidal irrigation and suction, with results obtained in 30 cases, Internat Surg Digest, 1929, *VII*, 3
- 4 HART, DERYL Empyema in children Report of 36 cases treated by tidal irrigation and suction, South Med Jr, 1930, *LXIII*, 823
- 5 HART, DERYL Treatment of chronic empyema by tidal irrigation, suction, and thoracoplasty, Jr Thorac. Surg, 1932, *II*, 157
- 6 HART, DERYL Treatment of acute empyema, Internat Clin, 1935, *IV*, 185

CHEMOTHERAPY OF BACTERIAL ENDOCARDITIS¹

By DAVID A. KINSELLA, F.A.C.P., St. Louis, Missouri

THE treatment of bacterial endocarditis by chemical agents has been under consideration for many years, and the literature before sulfanilamide contains many reports of cures

The reproduction of the disease in dogs^{1, 2, 3} and its cure following the use of merthiolate intravenously⁴ and sulfanilamide orally⁴ created a hope that such agents could be successful in human cases. With the failure of merthiolate and the extended interest in the use of sulfonamide drugs in other fields of coccal infection, there has been renewed study of the use of these sulfonamide drugs in all forms of bacterial endocarditis

A glance at the literature of the past few years reveals many reports of cures,⁵⁻¹⁷ but curiously, many times as many failures, and of course only a small fraction of the number of failures is reported. This fact leads to a more critical attitude with regard chiefly to the validity of diagnoses in those cases reported as cures. For example, if a patient known to have a valvular heart disease becomes febrile during the puerperium and displays a positive blood culture which is removed following sulfanilamide, the case may still have been not one of endocarditis, but perhaps only of pelvic cellulitis

If there were a certain cure for bacterial endocarditis now there would be no need for further discussion. But practitioners all over the country have attempted to repeat the allegedly successful methods in their own cases, and having met with failure, approach the discussion with open mind and with some skepticism

The Diagnosis Every clinical report should reveal the evidence on which the diagnosis is based. The diagnosis cannot be established by declaration. The evidences of bacterial infection of the heart valve are

1 *Toxemia* This point has been well emphasized by Christian¹⁸ in a recent paper. Toxemia is evidenced by fever, weakness, pallor,¹⁹ and deterioration of the blood

2 *Increasing evidence of valvular defects* The increase in evidence is very important. Not only must murmurs be detected, but these murmurs must be getting more coarse in quality week by week. The speed of increase is marked in acute endocarditis, slow but definite in subacute endocarditis. Those rare cases of vegetations which form on the wall of the aorta or pulmonic artery can be excluded from this discussion

3 *Bacteremia* It is important that the blood culture be constantly positive. In rheumatic cases in which there is a bacteremia the colony count is usually low, but the colonies should be identified as belonging to the

* Read at the Boston meeting of the American College of Physicians, April 22, 1941

same strain of nonhemolytic streptococcus. Too many reports otherwise convincing, describe only one or two blood cultures.

4 Embolic phenomena are common but not always present at the time of observation. The petechiae of the skin and conjunctiva, and the deeper hemorrhagic lesions about the finger tips are the most common. These are assumed to be embolic. Less frequent are the more definitely embolic occlusions in the spleen, kidney, and brain.

5 Finally, a critical exclusion of other sources of bacteremia must be made.

If the literature is now reviewed with these criteria in mind, the number of apparent cures dwindles.

The discussion of chemotherapy is linked with the discussion of pathogenesis.²⁰ It is not necessary to be controversial on this point since it is probably true that as the disease is produced, so it is to be cured. In other words, the route used by the bacteria can also be used by the chemical agent. But pathogenesis has a bearing on the relation of fibrin to the bacteria, and so is worth considering in view of the alleged importance of fibrin in defeating the effect of treatment.

The idea has been advanced that fibrin protects the imbedded bacteria from the action of drugs.⁸ This was the basis for using heparin in an effort to prevent the formation of this protective fibrin.^{21, 22} The subsequent use of heparin met with failure.

There is another idea²³ that the vegetation develops as a result of bacterial plugging of fine capillaries in the previously damaged valve and then builds up from the interior of the valve and breaks through the necrotic material onto the free surface of the valve where some blood-stream fibrin deposits on its surface.

Studies of vegetations both in human and in experimental⁴ cases seem to support the idea that the bacteria causing the infection of the blood stream are not those imbedded in the mass of pink-staining material, but rather the bacteria spreading upon the endocardial surface uncovered by fibrin. This would give fibrin a more beneficent rôle as far as the patient is concerned, and would support the theory that the formation of fibrin should be encouraged rather than prevented.

In the medical service at the University Hospital of St. Louis University in the past three years there have been 28 cases of acute and subacute bacterial endocarditis treated with chemical agents. It has frequently happened that blood cultures were sterilized by both merthiolate and the sulfonamide drugs. Merthiolate should never be given in amounts exceeding 0.15 gram per 100 lbs. of body weight, nor more frequently than once in 10 days. This drug should not be used if there is evidence of active hemorrhagic nephritis.

In the use of the sulfonamide drugs an effort was made to maintain the usually accepted levels of concentration in the blood. Two patients have been treated with neoarsphenamine.

Of the 28 cases in this series, seven were of the acute or malignant variety, and 21 of the subacute variety All the latter were infected by non-hemolytic streptococcus There were no recoveries in this series (table 1)

TABLE I
Chemotherapy of Bacterial Endocarditis

	Drug Used	Result
Acute Bacterial		
Pneumococcus X	Sulfapyridine	Autopsy
I	" + Serum I	"
XII	" + Serum VII	"
III	Sod Sulfapyridine	"
VIII	Sulfapyridine	No autopsy
V	Sulfapyridine + Serum V	"
Gonococcal	Sulfanilamide + Fever	Autopsy Aortic Veg
"	Sulfapyridine	"
Subacute Bacterial		
Streptococcus Non-hem	Drug Used	
9 patients	Merthiolate	Autopsy
2 "	" + Sulf	Autopsy
1 "	" + Vaccine	"
3 "	Sulfanilamide	"
3 "	Sulfapyridine	"
1 "	Sulfathiazole	"
1 "	Sulf + Merth + Neoarsph	"
Total Number Treated Cases—28		No Recoveries

There were three patients whose histories deserve special mention The first illustrates how standard methods instituted under apparently ideal conditions, nevertheless failed to bring about recovery (table 2) The second

TABLE II
Chemotherapy of Bacterial Endocarditis, Special Cases of Bacterial Endocarditis

- (1) Male, 27, acute gonococcal arthritis
Sulfanilamide from fourth day enough to give continuous concentration in blood of 10 mg per 100 c c
Negative physical examination of heart by competent examiners
Positive blood culture on entrance
Three treatments by hyperthermia (physical)
Cardiac murmurs, appeared and increased
Autopsy Aortic gonococcal endocarditis
Pericarditis

illustrates the possible cure of endarteritis of the pulmonary artery by merthiolate (table 3) The third, a patient on the service of Dr W H Olmstead in St Mary's Hospital, illustrates the cure of bacterial endocarditis or endarteritis by successful ligation of a patent ductus arteriosus by Dr J M

TABLE III
Chemotherapy of Bacterial Endocarditis, Special Cases of Bacterial Endocarditis

- (2) Male, 14, no history of acute rheumatic fever
Systolic murmur and thrill, second left i c s
High diastolic pressure
Blood cultures 500, 540, 550 colonies per c c
Ligation of patent ductus arteriosus
Sterile blood cultures
Clinical recovery

Mudd This case will undoubtedly be added to the literature by these workers to take its place with one previously described by Touroff and Vessel (table 4)

TABLE IV

Chemotherapy of Bacterial Endocarditis, Special Cases

(3) Female, aged 23

Onset Sore throat treated with sulfanilamide
 Later, fever and pain in left chest
 Examination Systolic murmur second ics left
 Blood Cultures Non-hemolytic strep 17 times
 50 colonies per cc
 Clinical Diagnosis Subacute bacterial endocarditis
 pulmonic valve (congenital)
 Treatment Merthiolate
 Autopsy Healing pulmonary endarteritis—
 mercury poisoning

CONCLUSION

The practitioner in considering the chemotherapy of endocarditis must be sure, first, of the diagnosis. He must then avoid injuring the patient. He must select chemical agents which seem to suit his situation. These are in order of reported successfulness: sulfanilamide, sulfapyridine, sulfanilamide combined with fever physically induced, neoarsphenamine.

A few years more of observation are necessary to determine which of these procedures, if any, is to be uniformly or occasionally successful.

BIBLIOGRAPHY

- 1 KINSELLA, R. A., and SHERBURN, C. C. Experimental production of streptococcus endocarditis with glomerular nephritis, *Proc Soc Exper Biol and Med*, 1923, **xv**, 252-256
- 2 NEDZEL, E. Experimental endocarditis, *Arch Path*, 1937, **xxiv**, 143-200
- 3 FRIEDMAN, M., KATZ, L. N., and HOWELL, K. Experimental endocarditis due to *Streptococcus viridans*, *Arch Int Med*, 1938, **lxi**, 95-118
- 4 KINSELLA, R. A., and MUETHER, R. O. Experimental streptococcus endocarditis, *Arch Int Med*, 1938, **lxi**, 247-270
- 5 LIPPMANN, KURT. Subacute bacterial endocarditis case, new method of treatment, *New York State Jr Med*, 1940, **xxxix**, 524-528
- 6 COLVIN, LESLIE T., JR. Subacute bacterial endocarditis, apparent recovery, *Jr Michigan State Med Soc*, 1940, **xxxi**, 946
- 7 HEYMAN, J. J. Subacute bacterial endocarditis successfully treated with sulfanilamide, *Jr Am Med Assoc*, 1940, **cxiv**, 2373-2375
- 8 BIERMAN, WM., and BAEHR, G. Use of physically induced pyrexia and chemotherapy in treatment of subacute bacterial endocarditis, *Jr Am Med Assoc*, 1941, **cxvi**, 292-294
- 9 MAJOR, R. H. The effect of sulfanilamide compounds on endocarditis, *Am Jr Med Sci*, 1940, **clxxxix**, 758-768
- 10 ANDREWS, C. T. Bacterial endocarditis, possibility of cure by sulphonamides, *Brit Med Jr*, 1940, **i**, 722-725
- 11 DOCKERAY, G. C., and KAWERAN, E. Heparin in subacute bacterial endocarditis, *Brit Med Jr*, 1940, **ii**, 2703

- 12 SWAIN, R H A Strain variations in the resistance of *Streptococcus viridans* to sulphonamide compounds, Brit Med Jr, 1940, part 1, 722-725
- 13 ORGAIN, E S, and POSTON, M A Gonococcal endocarditis with recovery after sulfapyridine, New England Jr Med, 1939, ccxxi, 167-169
- 14 FUTCHER, P H, and SCOTT, B C Four cases of gonococcal endocarditis treated with sulfanilamide with recovery of one, Bull Johns Hopkins Hosp, 1939, lcv, 377-391
- 15 SAILER, S Subacute bacterial endocarditis treated with sulfanilamide resulting in granulocytopenia and death, Am J Clin Path, 1939, ix, 269-278
- 16 ELLIS, G R Treatment of subacute bacterial endocarditis with M & B 693, Lancet, 1938, ccxxxv, 1521-1522
- 17 SPINK, W, and CRAGO, F H Evaluation of sulfanilamide in the treatment of patients with subacute bacterial endocarditis, Arch Int Med, 1939, lxiv, 228-248
- 18 CHRISTIAN, HENRY A The developing clinical picture of subacute *Streptococcus viridans* endocarditis, Trans Assoc Am Phys, 1940, lv, 183-187
- 19 LIBMAN, E, and CELLER, H L The etiology of subacute infective endocarditis, Am Jr Med Sci, 1910, cxxxv, 516-527
- 20 KEEFER, CHESTER Pathogenesis of bacterial endocarditis, Am Heart Jr, 1940, xix, 352
- 21 FRIEDMAN, M, HAMBURGER, W W, and KATZ, L N Use of heparin in subacute bacterial endocarditis, Jr Am Med Assoc, 1939, cxiii, 1702-1703
- 22 KELSON, S, and WHITE, P A new method of treatment of subacute bacterial endocarditis, Jr Am Med Assoc, 1939, cxiii, 1700-1702
- 23 ALLEN, ARTHUR Nature of vegetations of bacterial endocarditis, Arch Path, 1939, xxvii, 661-671
- 24 SCHOTTMUELLER, H Endocarditis lenta, Munchen med Wchnschr, 1910, lvii, 617-620
- 25 BLAHD, M, FRANK, I, and SAPHIR, O Arch Path, 1939, xcvii, 424-432
- 26 MCNEAL, W J, SPENCE, M J, and WASSEEN, M Transmission of endocarditis lenta to rabbits, Proc Soc Exper Biol and Med, 1939, xxxv, 473-475
- 27 BAYNE-JONES, S The blood vessels of the heart valves, Am Jr Anat, 1917, xxi, 449-463
- 28 MARTIN, H E, and ADAMS, W L Bacterial endocarditis superimposed on syphilitic aortitis and valvulitis, Am Heart Jr, 1938, xvi, 714-727
- 29 SPINK, W, and NELSON, A A Brucella endocarditis, ANN INT MED, 1939, xiii, 721-728
- 30 SHILLING, M S Bacteriology of endocarditis with report of two unusual cases, ANN INT MED, 1939, xiii, 476-486
- 31 FORSTER, D Fatal bacterial endocarditis due to *Salmonella supestifer*, Am Jr Med Sci, 1939, clxxxvii, 234-240
- 32 UHR, N Bacterial endocarditis, Arch Int Med, 1939, lxiv, 84-90
- 33 WHITE, HAROLD J The relationship between temperature and the streptococcal activity of sulfanilamide and sulfapyridine in vitro, Jr Bact, 1939, xxxviii, 549-562
- 34 TOUROUFF, A S W, and VESELL, HARRY Experiences in surgical treatment of subacute *Streptococcus viridans* endarteritis complicating patent ductus arteriosus, Jr Thoracic Surg, 1940, x, 59

SPUTUM STUDIES IN PNEUMONIA. THE SELECTION OF THERAPY *

By ARTHUR W FRISCH, M D , and ALVIN E PRICE, M D , F A C P ,
Detroit, Michigan

DURING the past few years the sulfonamide drugs have proved to be so effective that they have largely supplanted serum in the treatment of pneumococcic pneumonia. Some clinicians, however, use both forms of medication either simultaneously in critically ill patients or separately in the event of failure of one agent alone. Because of the known differences in the mode of action of serum and chemotherapy, and because of variations in the severity of different cases, it would seem desirable to individualize specific treatment if some satisfactory criterion was available which would indicate the exact status of each patient. During the past four years we have been studying Wright stained smears of rusty sputum from patients with pneumococcic pneumonia in an effort to obtain information concerning the pneumonic process in the lungs of individual cases. Several observations made during this study which are of particular interest are summarized below. For the technic and detailed results the reader is referred to the original publications ^{1, 2, 3, 4, 5, 6}

It was noted that the number of extracellular encapsulated pneumococci in rusty or bloody sputum constituted a reliable index of the severity of the pneumonic process. This observation has made possible an accurate estimate of the prognosis in each case. A definite correlation was obtained between the number of pneumococci per oil immersion field in smears of the sputum and those clinical factors which are usually regarded as true indices of the severity of the infection. Thus, as the number of pneumococci per field increased a corresponding rise in mortality rate, incidence of bacteremia, leukopenia and multiple lobe involvement also occurred. If the sputum count exceeded 50 per field, the prognosis was usually grave regardless of what form of therapy was administered.

Examination of sputum has also revealed the difference in the mode of action of serum and chemotherapy as seen in human patients. Within 8 to 36 hours after the intravenous injection of specific horse or rabbit serum the pneumococci in the sputum were found to be agglutinated, and in many cases an increased phagocytosis of the organisms was demonstrable. The number of pneumococci per field, however, decreased gradually in most instances so that by the time the sputum lost its rusty character only a few

* Received for publication May 22, 1941

Departments of Bacteriology and Internal Medicine, Wayne University College of Medicine, Detroit, Michigan

Supported by a grant from the Commonwealth Fund to the Michigan Department of Health Laboratories

were present. Occasionally specimens of sputum from patients who had not yet received therapy contained pneumococci which were already agglutinated. In these cases it was believed that the spontaneous clumping was indicative of a developing active immunity on the part of the patient himself*. It was also observed that when serum was given to patients with large numbers of pneumococci in the sputum the induction of agglutination was difficult and in some cases a progressive increase in number of pneumococci occurred even in the presence of clumping and phagocytosis. Chemotherapy, on the other hand, usually accomplished that which serum often failed to do. Within 12 to 36 hours after the administration of sulfanilamide, sulfapyridine, or sulfathiazole the number of pneumococci per field in the sputum decreased rapidly. This effect was independent of the agglutination and phagocytosis associated with active or passive immunity. Occasional patients were encountered who failed to show a decrease in the

TABLE I
Method of Selecting Therapy

Pneumococci per Field	Day of Illness	Sputum Clumping	Treatment
10 or less	4 or more	—	No specific treatment
	Any	+	
10 or less	3 or less	—	Antipneumococcic serum
11 to 50	Any	+ or —	Sulfapyridine or sulfathiazole
51 or more	Any	+ or —	Chemo- plus serum therapy

number of pneumococci, but the majority of those treated with the three drugs responded with a typical bacteriostatic effect in the sputum. "Drug fastness" as judged by the return of the pneumococci to the sputum following an initial decrease was observed in 17 per cent of the patients treated with sulfanilamide, whereas the same phenomenon occurred in 6 per cent of those given sulfapyridine and in only 2 per cent of those treated with sulfathiazole†.

If the above observations were correct it ought to be possible to conduct a therapeutic experiment in which the patients are grouped according to prognosis on admission to the hospital and an adequate form of therapy selected for each patient by means of the sputum examination. We have accordingly treated 270 roentgenographically proved cases of types I, II, IV, V, VII, and VIII pneumonia in which the sole criteria for the selection of therapy were the sputum findings and clinical data listed in table 1. In such an experiment the lowest mortality rate would be expected in those cases which received serum or no specific treatment, whereas the highest mortality

* Studies in progress at the present time indicate that spontaneous clumping of pneumococci in the sputum is due to the production of agglutinins by the host.

† Evidence is now available which indicates that these drug fast strains are able to grow in concentrations of sulfapyridine and sulfathiazole exceeding those found in the patients' blood during therapy.

would occur in those patients who were given sulfonamide drugs or combined therapy. The important factors of age, pneumococcus type, bacteremia, leukopenia, and the degree of pulmonary involvement were not considered. Subsequent specimens of sputum were obtained at intervals of 12 hours to determine whether or not a therapeutic effect had been obtained, and the appropriate treatment was instituted if the number of pneumococci per field increased. Serum therapy was discontinued when clumps of pneumococci appeared in the sputum.³ During the past year we have also successfully controlled chemotherapy dosage by means of the sputum. The results of these observations will be reported in future communications.

RESULTS

In the group of 48 patients who received no form of specific therapy there were none in whom the blood culture was positive and only a few who had total leukocyte counts below 10,000 or who had more than one lobe of the lungs involved. All of these cases, on the basis of the method of selection used, showed 10 or less pneumococci per oil immersion field throughout their illness (table 2). Specific therapy was withheld in these patients

TABLE II
No Specific Therapy

Type	Cases	Bacteremia	Leukopenia	Multiple Lobe	Expired
I	18	0	2	1	0
II	4	0	0	1	0
IV	1	0	1	0	0
V	5	0	0	1	0
VII	8	0	1	2	0
VIII	12	0	0	1	0
Total	48	0	4	6	0
Per cent		0%	8%	13%	0%

because it was considered that either adequate immunity was present or the infection was mild enough to be kept in check by the natural defenses of the patients themselves. Although the clinical course in many of these cases was not dramatic, they all recovered satisfactorily from their illness.

In table 3 are included 70 patients who had been ill less than four days but who showed the sputum findings of a relatively mild infection (10 or less pneumococci per field). Since these patients had not been ill long enough to develop an active immunity, passive therapy in the form of specific serum was considered logical in order to prevent the development of a more serious pneumonia. It is interesting to note that although the bacteremic incidence in this group was 17 per cent and although the average dosage of serum for each patient was only 35,000 units, an amount usually considered insignificant in either bacteremic or non-bacteremic cases, there

were no deaths in the series. It is likely that many of these patients would have recovered without any form of specific therapy and probably all would have responded well to sulfapyridine or sulfathiazole. We considered, therefore, that the 118 patients who were not treated or given small doses of serum would have recovered with any form of therapy.

TABLE III
Serum Therapy

Type	Cases	Bacteremia	Leukopenia	Multiple Lobe	Expired	Average Serum Thousand Units
I	16	1	1	1	0	35
II	14	2	0	1	0	40
IV	1	0	0	0	0	40
V	6	2	0	0	0	34
VII	19	4	1	7	0	30
VIII	14	3	2	3	0	30
Total	70	12	4	12	0	35
Per cent		17%	6%	17%	0%	

As previously indicated, chemotherapy was reserved for the group of moderately and severely ill patients (11 to 50 pneumococci per field) who, in the past, had responded poorly or not at all to treatment with serum. The status of the immune mechanism was not considered because of its relative inefficiency in patients with large numbers of pneumococci in the sputum. The institution of an efficient antibacterial therapy was deemed necessary in order to reduce the number of organisms in the pneumonic exudate as quickly as possible. In 114 patients given chemotherapy alone (table

TABLE IV
Chemotherapy

Type	Therapy	Cases	Bacteremia	Leukopenia	Multiple Lobe	Expired
I	Pyridine	14	4	2	6	0
	Thiazole	24	7	1	9	3
II	Pyridine	10	6	2	4	0
	Thiazole	7	4	2	4	0
IV	Pyridine	2	0	1	2	0
	Thiazole	10	3	2	2	0
V	Pyridine	1	0	0	1	0
	Thiazole	7	4	0	3	0
VII	Pyridine	12	5	1	8	2
	Thiazole	11	5	4	8	0
VIII	Pyridine	10	4	3	4	1
	Thiazole	6	3	2	2	1
Total		114	45	20	53	7
Per cent			40%	17%	46%	6%

4) it should be noted that the bacteremic incidence and multiple lobe involvement were significantly increased over those found in the preceding two groups. However, the ultimate fatality rate of only 6 per cent in the presence of a 40 per cent bacteremic incidence would seem fully to justify the choice of therapy. The data also represent additional evidence for the

TABLE V
Serum Plus Chemotherapy

Type	Therapy	Cases	Bacteremic	Leukopenia	Multiple Lobe	Expired	Average Serum Thousand Units
I	Pyridine Thiazole	3	3	1	3	3	350
		3	3	1	2	1	
II	Pyridine Thiazole	2	1	2	2	2	380
		5	4	5	5	3	
IV	Thiazole	1	1	1	1	1	100
V	Thiazole	2	2	1	2	1	300
VII	Pyridine Thiazole	3	1	1	1	0	370
		4	4	3	4	2	
VIII	Thiazole	1	0	0	1	1	440
Total		24	19	15	21	14	323
Per cent			79%	63%	88%	58%	

therapeutic efficiency of sulfapyridine and sulfathiazole in moderately to severely ill patients

We considered that those patients with sputum counts exceeding 50 per oil immersion field were potentially overwhelmed by their infection. Although only 24 patients were placed in the above category, the majority of them showed blood stream invasion, low total leukocyte counts, and two

TABLE VI
Miscellaneous Cases

Original Rx	Cases	Bacteremia	Leukopenia	Multiple Lobe	Expired	Additional Reasons for	
						Rx	Rx
Serum	5	1	0	2	1	Chemo	Sputum Count
Serum	2	1	0	1	1	Chemo	Pericarditis
Serum	1	0	0	0	0	Chemo	Phlebitis
Chemo	1	1	1	1	0	Serum	Hemolytic anemia
Chemo	1	1	0	0	0	Serum	Pericarditis
Pyridine	1	1	1	1	0	Pyridine	Enthusiastic interne
Pyridine	2	1	0	2	0	Thiazole	Pneumococci pyridine fast
None	1	0	0	0	0	Chemo	Unexplained fever
Total	14	6	2	7	2		

or more lobes involved during their illness. They were given, accordingly, large doses of serum in addition to chemotherapy*. In spite of the intensive treatment the mortality rate (58 per cent) was considerably higher than that in the preceding three groups of cases.

Fourteen cases were placed in a miscellaneous group presented in table 6. Five patients received initial serum therapy, but in subsequent specimens of sputum the number of pneumococci had increased to more than 10 per field. Serum was, therefore, discontinued and chemotherapy substituted in its place. The forms of therapy given to the remaining nine patients and the reasons for the additional treatment are recorded in the last column of table 6.

DISCUSSION

A total of 270 cases was studied in which the bacteremic incidence was 30 per cent and the mortality rate was 9 per cent. The figures have not been corrected and, therefore, include all deaths from pneumonia and its complications irrespective of the duration of illness and the period of hospitalization. Approximately 50 per cent of the patients were considered as potential survivors under any form of treatment and only 10 per cent of them were characterized as potential deaths under any form of treatment. It should be pointed out that we did not believe that all patients received the most effective form of therapy. This is especially true in the group of 118 cases which were given either serum or no form of specific therapy. While the ultimate outcome was favorable, their clinical course, as indicated by temperature and pulse response, was frequently not dramatic. On the other hand serum plus chemotherapy was deemed necessary in only 10 per cent of the percentage studied. However, the results of combined therapy cannot be properly evaluated until they are compared with those obtained in a similar group of selected cases treated with sulfonamide drugs above. In the final analysis of the above and additional cases the clinical factors will be considered in detail.

Most clinical trials of therapeutic agents in pneumonia have been based primarily on the method of alternate case selection. In order to obtain significant results large numbers of patients must necessarily be studied. The method fails to take into consideration those cases which would survive under any form of therapy and discards the overwhelmingly ill patients who expire shortly after admission to the hospital. The classification of cases into prognosis groups by means of sputum examination appears to be a method of case selection which would permit a true comparison of the efficacy of various therapeutic agents. The results of the therapeutic experiment which have been presented strongly support this concept. We also believe that the sputum findings afford a method of recognizing severely ill patients on admission to the hospital so that combined therapy may be in-

* Most of the patients in this group received the sodium salt of sulfapyridine and sulfathiazole intravenously.

stituted immediately. Although such patients represent only a small percentage of the total cases of pneumonia, they, nevertheless, are responsible for the majority of fatal terminations. In addition to the above, sputum examinations are of value in determining whether or not chemotherapy is producing the desired bacteriostatic effect and in the detection of cases in which the pneumococci have become resistant to the drugs. We are also utilizing the sputum as a method of controlling the dosage and period of administration of both serum and chemotherapy. The results of the above studies will be presented in future communications.

SUMMARY

In a series of 270 typed cases of pneumococcic pneumonia the therapy for each patient was selected by means of sputum examination. The results which were obtained support the concept that the sputum findings may be used as a reliable aid in prognosis and also as a method of individualizing therapy for each patient.

BIBLIOGRAPHY

- 1 FRISCH, A. W. Sputum studies in pneumonia as an aid in prognosis, *Am Jr Clin Path*, 1940, x, 472
- 2 FRISCH, A. W. Sputum studies in lobar pneumonia phagocytosis and the effect of serum therapy, *Proc Soc Exper Biol and Med*, 1938, xxxix, 473
- 3 FRISCH, A. W. Clumping of extracellular encapsulated pneumococci in sputum for control of serum therapy, *Proc Soc Exper Biol and Med*, 1939, xl, 495
- 4 FRISCH, A. W. Sputum studies in pneumonia the effect of sulfanilamide, *Jr Lab and Clin Med*, 1940, xxv, 361
- 5 FRISCH, A. W. Sputum studies in pneumonia the effect of sulfapyridine and sulfathiazole, *Am Jr Clin Path*, in press
- 6 FRISCH, A. W., and PRICE, A. E. Sputum studies in pneumonia therapy and prognosis, *Detroit Med News, Wayne University Educational Issue No 1*, 1941, xxxii, 20

THE MEDICAL ASPECT OF ANKYLOSING SPONDYLITIS (MARIE-STRUMPELL) ¹

By W W HERRICK, M D , F A C P , and T LLOYD TYSON, M D , F A C P ,
New York, N Y

INTRODUCTION

LYING between the fields of internal medicine and the specialties is a borderland into which the patient may stray and be lost to adequate diagnosis and treatment. It is here that the larger number of medical mistakes are made. In this connection we, as internists, have been impressed by the frequency with which Marie-Strumpell, or ankylosing, spondylitis is unrecognized and mistakenly labelled. We are, furthermore, convinced of the importance of considering this somewhat rare malady in the diagnosis of any painful state of the torso or extremities. With a clear picture of the disease in mind and with ordinary laboratory and roentgenologic facilities at hand, its recognition is not difficult. Our experience suggests the desirability of presenting Marie-Strumpell arthritis less as an orthopedic and more as a medical problem, especially a diagnostic one. Such is the purpose of this paper.

HISTORICAL NOTE

This syndrome has been established by the studies of a very few men. If we regard priority, the name of Von Bechterew should be attached to the disease, since this observer published the initial description in 1892. Strumpell in 1897 and Marie in 1898 followed with reports of the characteristic clinical picture now bearing their names. It is of interest that Von Bechterew emphasized the disturbances of innervation, the pain and the paresthesias, hyperesthesias, paresis and atrophy of muscles, and the tenderness on percussion, many of these being among the rarer manifestations of the disease. Strumpell was the first to note the abnormal straightness of the spine. In contrast to Von Bechterew he was impressed by the slight amount or absence of pain. Bachman, who first stressed the involvement of the sacroiliac joints, found 60 examples of ankylosing spondylitis in an examination of 2,561 spines. This is a higher proportion than any other observer has reported. In a study of 98 cases Fischer found involvement of the lumbar spine in 96 per cent, of the dorsal spine in 89 per cent, and of the cervical spine in 54 per cent, while the sacroiliac joints were implicated in 79 per cent. In 29 per cent of the same series there were associated changes in the smaller joints of the extremities characteristic of rheumatoid arthritis. A classic contribution is Schmorl's necropsy study of 10,000 spines, among which number but eight examples of ankylosing spondylitis.

* Received for publication February 7, 1941

were found. This well illustrates the rarity of the condition, a finding in accord with general clinical experience.

The English literature of ankylosing spondylitis is meager. Elliott in 1905 described five cases, four of which followed gonorrheal infection. Buckley, who first noted the characteristic increase in the sedimentation rate, cited 60 cases, only six of which were women. Joseph Miller discusses briefly the importance of Marie-Strumpell arthritis in the diagnosis of chronic rheumatic disease of the spine. With these exceptions the disease has been passed by in silence, especially by the internist.

CLINICAL FEATURES

This disease has attracted our special attention during the past five years. During this period, in an office practice, we have recognized but 10 cases. We estimate this as about 0.2 per cent of all new patients. The rarity of the malady is, therefore, apparent. We have found that ankylosing spondylitis is about as common as gout in ambulant private patients in New York City. The important diagnostic features may be discussed.

In our experience the disease is most common in males in the fourth decade. The onset is insidious and the progress slow. There are, however, acute cases which are more easily recognized. The dominant symptom is pain. The feature of this pain is its variability and the vagueness with which even the most intelligent patient describes it despite its severity. In the same individual the pain varies in site, degree and character from one phase of the disease to another. It may be in the back, the hip or shoulder girdles or in the distribution of the sciatic nerve. Although it may be continuous, it does not maintain a constant pitch of intensity. Characteristically it is worse during the last hours of the night. Often the patient is awakened about four a.m. and passes the rest of his time in bed in discomfort. After the patient has had a hot bath and has been about for a few hours, the pain gradually subsides. Usually the least amount of pain is experienced during the afternoon and evening. Any sudden or violent movement such as sneezing or coughing greatly increases the pain. In rare cases pain is not a prominent feature and is reported only after cross-questioning. The great variability of the pain needs emphasis. Pain about the shoulder girdle often suggests that of a subdeltoid bursitis, that about the hip a *malum coxae senilis*, again, a sciatica. Root pains may suggest pleurisy, intercostal neuritis, renal colic, or even a surgical abdomen. Sensory changes, usually hyperesthesia, are rarely impressive. Muscular weakness is common, muscular atrophy occasional.

In the majority of cases the onset is insidious with exacerbations and remissions but the disease may begin acutely with agonizing sciatic or lumbar pain suggesting a mechanical rather than an infectious etiology.

Second in importance in symptomatology is stiffness. In this symptom there are two factors: the first, muscle spasm which is the result of pain,

the second, actual organic changes with more or less fixation of the joints. The joints involved are the sacroiliacs, the small posterior intervertebrals, and the costovertebrals. Almost always the sacroiliacs are the first to be affected. This explains the frequency of sciatic pain. The muscles in which spasm is most obvious are the extensors of the spine. Undoubtedly the flexors are affected in like manner since motion in all directions is limited. When the cervical spine is involved, there is inability to rotate the head. This gives a very characteristic movement on attempting to look to the side and backward, since the entire torso turns with the head. The resulting gesture is almost diagnostic. The dorsal and lumbar spine may be more or less rigid so that movements of flexion and rotation are curtailed.

One of the most striking symptoms is rigidity of the thoracic cage. This results from involvement of the costo-vertebral joints and is shown in the lack of expansion of the chest on inspiration. Respiration is entirely diaphragmatic. It is interesting that the ribs tend to be fixed in an expiratory rather than an inspiratory position, the opposite of that seen in emphysema. To some extent these changes account for the curious and characteristic posture assumed by these patients. The head is carried forward, the chin depressed. With this is a moderate dorsal kyphosis and a flattening of the anterior chest. A lowered vital capacity results with lessened bellows effect of the lungs and consequent disadvantage to the circulation. A striking effect of the loss of flexibility of the lumbar spine is a lessening of the normal lumbar lordotic curve with a flattening of the lower back. To this muscular spasm contributes. When, as is frequently the case, the shoulder and hip joints are involved, stiffness can be demonstrated here. It is of interest that the process rarely affects any of the smaller joints of the extremities. In most cases the disease begins in the lumbar spine and extends upward but occasionally the cervical spine is first involved. Of the local manifestations tenderness is of considerable importance diagnostically. This is most common over the sacroiliac joints and the spinous processes. It is not always present. In some cases characteristic tenderness may be elicited by percussion over the spine or pelvic bones rather than by pressure.

Certain general symptoms occur in all but the most recent cases. There is loss of weight, of strength and of general muscle tone. In many cases the loss of weight is extreme, amounting to 40 or 50 pounds within a year. In such the question of malignancy, tuberculosis or other wasting disorder naturally is raised. Fever may be absent, or slight, rarely exceeding 101° F. The pulse is rapid as a rule, averaging 90 to 100 per minute. There is occasional anorexia. The mental aspect of these patients deserves notice. They seldom smile. There is a uniform dejection and depression. It is difficult to be sure that this is not other than one might expect in any chronic painful disease. To us, however, it has seemed to have certain features that become characteristic when observed in association with the typical attitude and posture of these patients. Rheumatic nodules are never

found. An occasional case will exhibit an endocarditis or an iritis which cannot be distinguished from those of rheumatic fever. Such findings imply a relationship between rheumatic fever and Marie-Strumpell arthritis.

ROENTGENOGRAPHIC FINDINGS

These are diagnostic. The initial finding is a haziness of the sacroiliac joints with an increased bone production along the joint margins which eventually leads to bony fusion. In a later phase a similar process involves the posterior intervertebral joints of a portion or of the entire spine. In the most advanced stage there is a calcification of the anterior and lateral ligaments of the spine producing the typical bamboo appearance which is pathognomonic. A general decalcification of all bones may be seen, often quite early in the disease. It is important that the clinician remember that the roentgen-ray changes characteristic of the malady may be late in appearance and that pain, stiffness and other symptoms often precede roentgenologic findings by months or years.

LABORATORY FINDINGS

The laboratory is of very little aid in the diagnosis. The most constant finding is an elevated sedimentation rate. Typically, this varies between 30 and 80 mm. In contrast to the finding in rheumatoid arthritis, the streptococcus agglutinins are not increased. Secondary anemia is frequent. There are no characteristic changes in the leukocytes.

CASE REPORTS

Case 1 A male of 20 years who had suffered gradual onset of pain and stiffness in the distribution of the right sciatic nerve over a period of one year. Eventually the pain became severe enough to interfere seriously with the patient's rest, especially in the early morning hours. The only positive physical findings were a slight atrophy of the right thigh and decreased deep reflexes in that extremity. There was no stiffness of the spine. The sedimentation rate was 34 mm. The roentgenograms of the spine and hips were negative. A definite diagnosis was not made. With salicylates and rest there was apparent recovery. The patient was seen three years later, again complaining of the former symptoms with the addition of pain and slight stiffness in the lower back. Roentgen-ray study at this time was negative. The sacroiliac joints revealed no significant changes. An orthopedic consultant was of the opinion that the sciatica was due to an acute lumbo-sacral angle. A spinal fusion was advised. This recommendation was not followed. Again improvement followed medical treatment. Five years after onset the pain became so severe that the last half of the night was spent in serious discomfort. At this time examination showed definite stiffness in the lumbar and cervical spine, and for the first time the roentgenograms showed haziness in the sacroiliac joints. The rest of the spine was negative. The sedimentation rate was 27 mm. The diagnosis of Marie-Strumpell spondylitis was then made, six and a half years after the onset. The subsequent course has validated this diagnosis. A course of chrysotherapy was without benefit. Radio-therapy and general measures, including rest, have been followed by moderate improvement.

Case 2 A man of 53 years who complained of dyspnea and of recurrent attacks of pain and stiffness in the lower back. Occasionally these attacks were quite severe and associated with pain and stiffness in the hips and shoulders. Physical examination revealed the murmurs of mitral stenosis and of aortic insufficiency. These had been reported during the past 25 years. Stiffness of the lumbar and dorsal spine was present. Roentgenograms showed calcification of the lateral ligaments of the dorsal spine with haziness of the posterior intervertebral joints. The sacroiliac articulations were relatively normal. The sedimentation rate was 22 mm in one hour.

Case 3 A woman of 55 years who complained of severe but intermittent low back pain of one month's duration following an unusual strain in lifting a heavy object. Similar though milder attacks had been suffered in the past. The physical examination revealed a markedly spastic and rigid spine painful on the least motion. The severity of the symptoms and the acuteness of the onset suggested either an osteomyelitis, neoplasm or serious mechanical derangement of the spine. The temperature was 100° F, orally, and the sedimentation rate was 55 mm. Roentgen-rays of the spine made the diagnosis evident in calcification of the lateral ligaments, sacroiliac arthritis and generalized decalcification of all bones.

Case 4 A man of 36 years with a five year history of pains in the thighs, hips and shoulders, of occasional attacks of sciatica, and of loss of energy and strength. The onset was acute, with fever reaching 102° F, and lasting about two weeks. Since then, symptoms have been more or less continuous, but of varying severity, never incapacitating. The physical examination disclosed definite limitation of motion in both the lumbar and cervical spine. Roentgenologically there was generalized decalcification of bone, calcification of the anterior longitudinal ligament in the cervical region and haziness of the sacroiliac joints. A sedimentation rate was not recorded in this case.

Case 5 A man of 38 complained of waking in the early hours of the morning with stiffness and pain in the mid-back and shoulders. This was relieved by aspirin and by pacing the floor, after which he was able to return to sleep in from one-half hour to two hours. These symptoms, which had been present for 10 years, were variously ascribed to spastic colon, lumbago and sciatica. A chance finding of hematuria on one occasion had raised the question of renal pathology, but repeated cystoscopic and other studies had been negative. The physical examination revealed only stiffness of the lumbar spine with pain on attempting flexion. The sedimentation rate was 10 mm. Roentgen-rays of the spine showed destruction of the right sacroiliac joint with marginal sclerosis, obliteration of the posterior intervertebral joints of the lumbar spine, and generalized decalcification. The subsequent course has been unsatisfactory because of increasing pain and stiffness in the spine.

Case 6 A man of 32 who complained of stiff and sore back muscles with occasional attacks of sciatica of six years' duration. He noted that sneezing particularly provoked severe pains in the back and chest. Sleep was disturbed by the pain during the early morning hours. Recently there had been a decrease in chest expansion, and a rigidity of the spine. The sedimentation rate was 40 mm. Roentgen-rays showed complete fusion of the sacroiliac joints and obliteration of the small posterior intervertebral joints of the thoracic and lumbar vertebrae. It is interesting that this patient's father also had a poker spine.

Case 7 A man of 50 who gave a history of arthritis of the spine of 17 years' duration associated with recurrent attacks of severe iritis. The arthritis and iritis began at the same time and a flare-up of the one was always associated with increased activity of the other. In recent years the neck had also become stiff so that the entire spine was a rigid fixed unit. Due to fixation of the chest in the expiratory position dyspnea had been present on exertion. Physical examination disclosed a classical poker spine and many adhesions of the iris. Roentgenograms disclosed a bamboo

spine with complete replacement of the sacroiliac joint spaces by bone. The sedimentation rate was 80 mm in one hour.

Case 8 A woman of 32, with a history of 15 years of recurring attacks of low back and left sciatic pain. These attacks occurred without warning and were severe and crippling. The patient was found to be in severe pain with back held rigid, any motion causing agonizing paroxysms. The lumbar muscles were board-like in their rigidity. The sedimentation rate was 30 mm in one hour. Roentgen-rays of the spine were negative save for a moderately advanced sacroiliac arthritis, and generalized osseous decalcification. Radio-therapy gave prompt relief.

Case 9 A man of 36 years with a history similar to that of case 8. For 10 years he had noted pain and stiffness in the lower back, with periods of exacerbation and remission. There had been some weight loss. During this time no definite diagnosis had been made. Several observers had suggested that some obscure systemic disease might be responsible. Physical examination showed moderate limitation of motion in the lumbar spine. The sedimentation rate was 30 mm in one hour. Roentgen-rays revealed definite blurring of the sacroiliac joints and of the posterior intervertebral joints of the lumbar spine in addition to a generalized decalcification of all bones.

Case 10 Spondylitis began at the age of 30 and was very severe, painful and crippling. The accepted diagnosis was Pott's disease. A plaster jacket was worn without relief. Finally a spinal fusion was done. After this there were five years of disability because of prostration and active symptoms. For several years after this pain continued, later it gradually disappeared. The patient on examination presented the characteristic aspect of ankylosing spondylitis in its quiescent end stage with poker spine and lack of thoracic respiration. Roentgen-rays showed operative fusion of the lower lumbar vertebrae and spondylitic fusion of the thoracic vertebrae. The patient felt that the course of his disease was not altered by the spinal fusion. He was convinced that the surgical procedure subjected him to much needless suffering and inconvenience.

TREATMENT

The disease should be managed as a chronic infection. A regimen such as one might enforce in tuberculosis in a latent stage is applicable in the treatment of ankylosing spondylitis. Fatigue is to be avoided, nervous stress and strain reduced to a minimum, long rest periods prescribed. If the patient must work, week-ends in bed are a desirable compromise. A long stay in the tropics especially in the cold months is most helpful. The patient's nutrition should be improved by a high caloric diet supplemented by ample vitamins. Large amounts of vitamin D are especially desirable. Crude cod liver oil, if tolerated, should be given in large amounts. If anemia is present vitamin B in addition to iron is indicated. Salicylates, aspirin or, temporarily, codeine are useful to control the pain. Prolonged hot baths, turpentine stupes, and diathermy are further measures. Pains should be taken to preserve as erect a posture as possible because of the inevitable fixation of the spinal joints as the disease progresses. The patient should sleep on a hard bed with a sheet of plywood between mattress and springs, if possible without a pillow. A plaster jacket in which to sleep and a leather jacket worn as a brace in some instances are valuable measures. On the whole chrysotherapy has been valueless in this syndrome.

PROGNOSIS

The disease rarely shortens life. Gradually after years the acute symptoms subside and the patients are left with the end stage structural changes in the affected joints. These cause varying degrees of disability from stiffness. The patients seldom stir with alacrity. They continue to show the attitudes and patterns of movement so characteristic of the disease. Pain is minimal or absent. In the average case one finds a satisfactory adjustment to life on a somewhat lowered level of activity.

SUMMARY

In summarizing the experience of internists in the diagnosis of ankylosing spondylitis we would emphasize the following points:

The disease is rare. Probably the majority of cases are undiagnosed. Many are wrongly diagnosed and wrongly treated. Perhaps the greatest error is the subjection of many of the victims of this disease to spinal fusion—a measure as futile as it is severe. As in so many other situations, diagnosis depends largely upon keeping the syndrome in mind when the problem of spinal disease comes up for consideration.

The penchant of ankylosing spondylitis for the male in the third to the fifth decade, the great variability of the symptoms, the lack of definition in localizing and describing the pain, its intermittent character, the peculiar attitudes and movements of the patient, the immobility of the thoracic cage, the slight or absent fever, the stiffness of the spine and the abnormal straightening of its lumbar segment, the roentgenographic findings, the elevated sedimentation rate, the occasional involvement of the smaller joints of the extremities and the rarer event of an endocarditis of the rheumatic type, all are important diagnostically. If the physician is alert to this picture, confusion with other pathologic states is unlikely. Naturally one must differentiate other diseases of the spine, among which one may mention late rickets, Pott's disease, prolapse of a nucleus pulposus, osteoarthritis, malignant disease of the bone or cord, sciatic neuritis, Paget's disease and osteomyelitis.

BIBLIOGRAPHY

- 1 BACHMANN, A (BARMBECK) Ein Beitrag zur Spondyloarthritis ankylopoietica, *Fortschr a d Geb d Rontgenstr*, 1930, xliii, 500-509
- 2 BUCKLEY, C W Ankylosing spondylitis in reports on chronic rheumatic diseases, 1935, H. K. Lewis and Co, Ltd, London, No 1, pp 77-89
- 3 ELLIOTT, G R Rigid spine. A study with report of five cases. *Autopsy, Am Jr Orthop Surg*, 1906, iii, 303-345
- 4 FISCHER, ANTON *Rheumatismus und Grenzgebiete*, 1933, Julius Springer, Berlin
- 5 MARIE, P Sur la spondylose rhizomelique, *Rev med*, 1898, xviii, 285
- 6 MILLER, J L Chronic rheumatic diseases of the spine, *Arch Int Med*, 1934, liv, 161
- 7 SCHMORL, G, and JUNGHANS, H Die gesunde und kranke Wirbelsaule im Roentgenbild, 1932, Georg Thieme, Leipzig

- 8 VON BECHTEREW, W Von der Verwachsung oder Steifigkeit der Wirbelsäule, Deutsch Ztschr f Nervenheilk, 1897, 21, 327-337 Ueber ankylosirende Entzündung der Wirbelsäule und der grossen Extremitätengelenke, Ibid, 1899, xv, 37-44 Neue Beobachtungen und pathologisch-anatomische Untersuchungen über Steifigkeit der Wirbelsäule, Ibid, 1899, 21, 45-57 I Originalmittheilungen I Steifigkeit der Wirbelsäule und ihre Verkrümmung als besondere Erkrankungsform, Neurol Centralbl, 1893, 21, 426-434
- 9 STRUPPELL, ADOLF Bemerkung über die chronische ankylosirende Entzündung der Wirbelsäule und der Hüftgelenke, Deutsch Ztschr f Nervenheilk, 1897, 21, 338-342

RHEUMATISM AND ARTHRITIS

REVIEW OF AMERICAN AND ENGLISH LITERATURE FOR 1940

(Eighth Rheumatism Review) *

By PHILIP S HENCH, M D , F A C P , *Rochester, Minnesota*, WALTER
BAUER, M D , F A C P , *Boston*, EDWARD BOLAND, M D , *Los Angeles*,
M. HENRY DAWSON, M D , *New York*, RICHARD H FREYBERG,
M D , *Ann Arbor*, W PAUL HOLBROOK, M D , F A C P ,
Tucson, J ALBERT KEY, M D , F A C S , *St Louis*,
L MAXWELL LOCKIE, M D , F A C P , *Buf-
falo, New York*, and CURRIER McEWEN,
M D , F A C P , *New York*

CONTENTS

General incidence of rheumatic diseases	1003
Classification of diseases of joints and related structures	1003
Diseases of joints related primarily to trauma	1003
Gonorrheal arthritis and gonorrheal rheumatism	1005
Tuberculous arthritis	1009
Pneumococcal arthritis	1011
Syphilitic arthritis and synovitis, Charcot (tabetic) joints	1011
Brucellosis undulant (Malta) fever	1012
Suppurative arthritis	1014
Rarer forms of specific arthritis	1015
Rheumatic fever	1016
Rheumatoid (infectious, atrophic) arthritis	1026
Still's disease	1050
Osteoarthritis degenerative joint disease	1051
Backache and sciatica	1055
Rheumatoid (ankylosing) spondylitis	1060
Osteo-arthritis (hypertrophic) spondylitis	1062
Gout and gouty arthritis	1062
Psoriatic arthritis	1066
Hemophilic arthritis	1067
Endocrine arthritis	1067
Miscellaneous types of joint disease	1068
Diseases of bursa	1071
Diseases about the shoulder joint the painful shoulder	1071
Diseases of muscles and fibrous tissues	1073
Fibrositis	1073
Miscellaneous conditions	1075
Other studies on joints and related tissues	1076
Rheumatism and the war	1079
Campaign against rheumatism	1081

* Received for publication November 3, 1941

This Review was prepared by the Editorial Committee (Dr Hench, chairman) of the American Rheumatism Association. The editorial comments express the opinions of the Editorial Committee, the authors of the Review, not necessarily those of the Association.

GENERAL INCIDENCE OF RHEUMATIC DISEASES SOCIAL AND ECONOMIC IMPORTANCE

The appalling morbidity and invalidism produced by rheumatic diseases in the United States and abroad were again emphasized by Snyder and others^{433, 435, 448} More than 320,000 otherwise able persons in the United States are rendered unemployable for an entire year by these disorders, the greatest incidence occurs among persons without maintenance incomes⁴⁴⁸ Calling arthritis "a neglected disease," Snyder urged physicians and laity to appreciate fully its sociologic and economic importance and to provide adequate facilities for the care of its many victims

New data from the National Health Survey^{66, 67} indicated that rheumatic diseases were the sixth greatest cause of disability among persons surveyed The rheumatic diseases ranked third among those which disabled persons for a year or more The incidence of rheumatic diseases was related to the annual family income, it was 3.5 times as great among persons on relief and twice as great among those whose family income was less than \$1,000 as among those who had a family income of \$3,000 or more⁶⁷

DEFINITION OF "RHEUMATISM" AND THE "RHEUMATIC DISEASES"

No new definitions of rheumatism and rheumatic diseases appeared Admittedly a poor term, "rheumatism" still remains the best word by which to refer to that great group of diseases, the "rheumatic diseases" characterized largely by pain in ligaments, muscles or joints⁵²⁴

CLASSIFICATION OF DISEASES OF JOINTS AND RELATED STRUCTURES

Differentiation of the rheumatic diseases was considered the first requisite for their accurate clinical investigation and therapy^{448, 503, 524} Remarks on various classifications were made^{435, 448, 464, 503, 524}

At its June, 1941, meeting the American Rheumatism Association adopted the following provisional classification (1) specific infectious arthritis (organism known), (2) arthritis of rheumatic fever, (3) rheumatoid arthritis (synonyms atrophic, proliferative and chronic nonspecific infectious arthritis, Still's disease, Marie-Strumpell spondylitis), (4) osteoarthritis (synonyms degenerative joint disease, hypertrophic, senescent arthritis), (5) arthritis of immediate traumatic origin, (6) arthritis of gout, (7) arthritis of neuropathic origin (Charcot's joint), (8) neoplasms of joints, (9) miscellaneous forms (or arthritis associated with other diseases)

DISEASES OF JOINTS RELATED PRIMARILY TO TRAUMA

Traumatic Arthritis and Synovitis Of 483 injuries of knees sustained in sports 203 resulted in ligamentous strains, 145 in joint contusions, 78 in muscular contusions, 43 in internal derangements, eight in bursal contusions and six in superficial contusions⁵⁷⁴ Differential diagnosis is often difficult, prognosis should be reserved until 24 or more hours after injury

Sprains and Strains Ligamentous sprains produce tears and hemorrhages in tissues and must be followed by absorption of hematoma and repair of tissue. Treatment should be aimed toward minimizing the hematoma.⁵⁷⁴ Thorndike recommended the immediate application of ice water, then the use of a compression sponge rubber bandage and rest. Convalescent treatment consists of heat, gentle massage and early weight bearing, the joint being supported by a compression bandage.

Internal Derangements of Knees The mechanism of injury is similar in most cases: internal torsion of femur on tibia with the knee in partial flexion. In the cases of Ferguson and Thompson 52 per cent of such injuries occurred in competitive sports, football accounted for 29 per cent. Symptoms of the various internal derangements are similar, diagnosis cannot always be established definitely before operation.⁶⁰² Aspiration may help to determine the amount of intra-articular injury; hemarthrosis indicates a tear of some intra-articular structure. Aspiration and "fixation with function" should constitute preliminary treatment. Recurrence of disability, especially locking, effusion and instability, warrants operative intervention.^{188, 260, 602} If the internal derangement is of long standing, secondary osteo-arthritis may be expected, such changes were found in 47 per cent of Wilmoth's cases.

The commonest internal derangement of the knee is damage to the internal semilunar cartilage. Of 121 patients who were operated on for this condition 105 were found to have the internal semilunar cartilage involved alone, 12, the lateral cartilage alone, and four, both the internal and lateral cartilages.⁶⁰² Manipulations under anesthesia, with reduction of the dislocated cartilage, were followed by recurrence in every case of Ferguson and Thompson who advised early surgical intervention in any knee with true locking. But Henderson did not recommend operation until locking had occurred several times; his surgical treatment resulted in "complete relief" in 77 per cent of cases, "improvement" in 15 per cent.

Hypertrophy of infrapatellar fat pad without injury to cartilage comprised 16 per cent of the internal derangements seen by Ferguson and Thompson. Symptoms were pain, effusion, limitation and instability. Preoperative diagnosis was usually incorrect. Excision of the fat pad gave relief in 75 per cent of cases.

Derangements from osteocartilaginous loose bodies may be due to osteochondritis dissecans, osteochondromatosis or osteo-arthritis.²⁶⁰ Osteochondritis dissecans was thought to be caused by the blocking of an end artery with consequent aseptic necrosis of a portion of bone and cartilage and the subsequent breaking off of a wandering osteocartilaginous fragment. Osteochondromatosis was considered to be a benign neoplastic process with the bodies originating in synovial membrane. Both conditions occur in young persons, operative results are excellent.²⁶⁰ Surgical removal of osteocartilaginous bodies due to osteo-arthritis in elderly persons was not advised unless troublesome locking occurs.

Penetrating Wounds of Joints Early excision of damaged tissue, removal of clots and fluid and irrigation of joint space (if contaminated) with pure ether were recommended by Ferguson and Dangerfield for penetrating wounds of the knee. Air aspirated into a joint through a superficial wound may erroneously suggest a gas bacillus infection.⁵⁸³ Even though not infected, foreign bodies (bullet, glass, needle) if not removed from joints may

cause progressive degenerative arthritis Key reported six such cases Foreign bodies in or near joints should be removed before degenerative changes result, except in intervertebral joints where fusion is asymptomatic

GONORRHEAL ARTHRITIS AND GONORRHEAL "RHEUMATISM"

Incidence There is no evidence that the incidence of gonorrhea has been materially reduced since the introduction of the sulfonamide compounds But some believe that complications of the disease have diminished At one hospital the yearly incidence of gonorrheal arthritis has been more than halved⁵³⁰

Among women with gonorrhea seen by Salberg, Brunet and Koch^{76, 487} gonorrheal arthritis developed in only 0.5 to 0.8 per cent Carpenter and Westphal studied the problem of the gonococcus carrier To eliminate the possibility of reinfection, they studied male inmates of a penal institution (Attica, New York) where supervision is rigid and the average sentence five years Among 1,061 inmates examined (937 white, 124 colored) 35 per cent of the whites and 50 per cent of the negroes gave a history of gonorrhea Pelvic organs were carefully examined, smears and cultures were prepared from urethral exudate, prostatic secretion, urinary sediment and anal discharge No acute infections were noted Eleven carriers were found, all white Three had symptoms and eight had signs of the disease From each carrier, *Neisseria gonorrhoeae* was isolated in culture from varying sources Smears were negative except in one case The longest proved carrier state (measured only from time of prison entry) was seven years and two months, others were weeks to one, two, and three years Extragenital and homosexual infection seemed to be ruled out by the physical surroundings and use of individual toilets The 11 carriers represented 2.8 per cent of men with a positive history and 1 per cent of the inmates examined Seven of the 11 carriers continued to harbor the gonococcus despite long, vigorous treatment, including sulfanilamide

[The paper is excellent and reemphasizes the value of cultural methods It shows conclusively that for years a person can have a low-grade carrier-state, difficult to overcome, also that a focus for the possible development of gonorrheal arthritis can smolder indefinitely—Ed.]

Clinical Data Usual features of gonorrheal arthritis were exemplified in reports of about 300 new cases^{25, 122, 141, 148, 202, 488, 487, 530} Proved monarticular gonorrheal arthritis in an infant (three weeks old) was successfully treated with sulfanilamide⁴⁸⁸ The mother had suffered from mild gonorrheal arthritis one week before delivery Reported cases of gonorrheal arthritis of the newborn were reviewed Gonorrheal polyarthritis developed in a child eight months old, shortly after it was given blood transfusions from its mother who for nine years had had arthritis, "a sequel to gonorrhea" Gonococci were recovered from the child's synovial fluid but not from the mother's blood¹⁸⁸

Keratosis blennorrhagica is a distinct entity characterized by gonorrhea, cutaneous keratosis and polyarthritis It occurs about once in 5,000 to 7,500 cases of gonorrheal urethritis Only 93 cases have been collected from the literature Combes, Dietrich and Cohen added two more cases The arthropathy usually precedes the skin lesions, and differs from the usual gonorrheal monarthritis in the simultaneous involvement of several

joints, chiefly knees, ankles, wrists and acromioclavicular joints Pain is severe but redness and periarticular edema are less than in gonorrheal monarthrititis or in rheumatoid arthritis Of all remedies used, fever therapy has given best results In two cases resistant to the sulfonamides skin and articular lesions rapidly disappeared during the use of the inductotherm

Diagnosis No new diagnostic aids were described

Pathology No studies on this subject were reported

Roentgenograms A feature regarded by an Italian physician as diagnostic in early gonorrheal arthritis was mentioned ⁴⁸⁴ [The original articles by Lupo, 1935 to 1939 should be consulted—Ed] No new data were contained in two other reports ^{194, 529}

Laboratory Data A well organized, discriminative collection of experimental and clinical data devoted largely to the biology of the gonococcus and its infections was published by the United States Public Health Service ⁵⁷⁰ It contains valuable information concerning laboratory procedures discussed later

1 *Identification of Gonococci in Smears* No new technic was proposed

2 *Cultures of Gonococci* Shaw and McAllister recommended washing ascitic fluid agar plates with tetra methyl-p-phenylene diamine hydrochloride, after 48 hours' incubation, to aid in identifying gonococcic colonies The resulting oxydase reaction immediately turns colonies purple, later deepening to black These colonies then are stained with Gram's stain, examined and subcultured on appropriate media for identification [The authors admitted that this reaction is not specific for gonococci, *Escherichia coli*, *Bacillus coli* and *Bacillus subtilis* show the same but less intense staining—Ed] Dienes ¹⁶¹ observed that certain cultures of gonococci, before disintegrating, swell up into large, deeply stained, spherical bodies If these cultures are kept one to two days at 25° C, a slight secondary growth appears in the agar below the colonies This growth consists of fine filaments and small granules which disintegrate rapidly These secondary forms resemble the "L₁ colonies" of *Streptobacillus moniliformis* Attempts to separate these secondary colonies from the parent organism failed

[These forms may represent a complex method of degeneration of the gonococcus, or perhaps a filtrable form of the organism exists, which may be carried from focus to joints The inability to grow these tiny forms separately may fit in with the known fact that it is impossible to culture organisms from some gonorrheal joints—Ed]

3 *Gonococcal Complement Fixation Tests* DiGioia refined the complement fixation test Others ^{25, 81, 141, 148, 202} considered the test useful in diagnosis

4 *Comparative Value of Laboratory Tests* The cultural method is superior to all others in diagnosing gonococcic infections ^{96, 186, 446, 570}

THE TREATMENT OF GONORRHEAL ARTHRITIS AND GONORRHEA

The literature of 1940 confirmed previous reports ^{5, 6, 7} that chemotherapy is best for gonorrhea and its complications Some physicians claimed a greater percentage of cures from the use of local therapy plus a sulfonamide compound, a few preferred hyperpyrexia plus chemotherapy

It is impossible to evaluate the respective merits of various treatments, because most investigators do not require rigid criteria of cure Only a few make cultures, most workers depend on smears, some are content with the disappearance of signs and symptoms, or absence of shreds in the "two glass

urine test" If only those reports based on rigid criteria of cure were accepted little could be written about the efficacy of sulfonamide compounds in the treatment of gonorrhea Other difficulties encountered in making therapeutic evaluations were noted in last year's review Adherence to a proposed plan devised for the rapid appraisal of chemotherapy in gonorrhea would greatly improve this deplorable situation¹⁴⁰ It is gratifying to note that most of the worthwhile reports are contributed by the United States Public Health Service

Before discussing further the treatment of gonorrheal arthritis we shall review briefly the general topic of sulfonamide compounds

Sulfanilamide and Its Derivatives, General Comment The present status of chemotherapy,^{384, 479} the relative value of sulfonamide compounds,⁴⁴⁵ and the nomenclature of modern chemotherapeutic drugs^{189, 290} were discussed New data on the action, and toxic and therapeutic effects of the sulfonamides are presented herein

1 Mode of Action From the following case Nesbit concluded that the site of action of sulfapyridine in genital gonococcal infections is in tissues, since the urine was evacuated via the bowel A patient who had previously had a ureterosigmoidostomy contracted gonorrhea and later prostatitis and epididymitis developed He was cured in eight days with 23 gm of sulfapyridine No new theories as to the mode of action of the sulfonamides were advanced⁴⁷⁹

2 Absorption, Diffusion and Excretion Long, Haviland and Edwards noted that sulfathiazole is absorbed and excreted faster than sulfapyridine, but is not as well conjugated by tissues They concluded that administration of the drug every four hours is necessary to maintain a constant level of sulfathiazole in blood

3 Toxic Reactions The acute toxicity of sulfathiazole for mice is a third greater than that of sulfanilamide and about half that of sulfapyridine, sulfathiazole methyl and sulfathiazole phenyl³⁸⁷ Long and his colleagues³⁸⁸ wrote an excellent article on the incidence of toxic reactions among 1,000 patients given sulfanilamide, 297 given sulfapyridine and 271 given sulfathiazole, it was reviewed last year [They failed to state that liver damage may result from these drugs, with hypoprothrombinemia and bleeding as the first evidence thereof—Ed] In one case edema of the uvula developed on the fifth day of sulfanilamide treatment, the patient failed to respond to administration of epinephrine and withdrawal of the drug, amputation of the uvula was performed⁶¹³

[It is impossible to determine from the data given the exact cause of the edema—Ed]

Sulfanilamide in Treatment of Gonorrheal Arthritis The treatment of gonorrheal arthritis with sulfanilamide was discussed^{25, 31, 75, 76, 141, 148, 202, 241}

^{438, 539} Sulfanilamide was generally preferred to other compounds [Some of us prefer sulfathiazole—Ed] Results were similar to those reported in the last Review about 70 to 85 per cent of patients were cured or markedly improved Culp considered mercurochrome given intravenously, as effective as sulfanilamide

Sulfapyridine in Treatment of Gonorrhea and Gonorrheal Arthritis No article devoted exclusively to the treatment of gonorrheal arthritis with sulfapyridine appeared Sulfapyridine was considered by Bauer and Short to be inferior to sulfanilamide for gonorrheal arthritis

With the administration, on the average, of doses of 3 gm a day during the first week and 15 gm per day the second week, and with dependence on smears as the criterion of cure, cures were recorded in 74 to 90 per cent of cases of gonorrhea and its complications^{12, 77, 272, 377, 414, 450, 542, 567, 601, 607} Rawlins, employing cultures as the criterion of cure, with follow-up periods of six months, reported cures of cases in 96 per cent Ferguson, Buckholtz and Hingson, employing the same rigid criteria of cure, treated 100 patients not cured by sulfanilamide, 75 per cent of them were cured by sulfapyridine in an average of seven days They concluded (1) inadequate treatment with sulfanilamide raises the resistance of the patient's infection toward sulfapyridine, (2) sulfapyridine is superior to sulfanilamide

Sulfathiazole in Treatment of Gonorrhea There were no reports on the treatment of gonorrheal arthritis with sulfathiazole

Sulfathiazole in adequate doses (4 gm or more per day) was used in the treatment of gonorrhea^{27, 141, 384, 380} Some physicians compared it favorably with sulfanilamide¹⁴¹, others believed it better than sulfanilamide^{27, 384, 380} Sulfathiazole is preferable to sulfamethylthiazole^{384, 380} for the latter may cause serious peripheral neuritis

Other Sulfonamide Compounds in Treatment of Gonorrhea and Gonorrheal Arthritis By several workers sulfanilyl-sulfanilamide (disulon) was considered superior to sulfanilamide^{18, 46, 291, 582} [None of these workers required negative cultures as a criterion of cure—Ed] Six patients who had sulfanilamide-resistant gonorrhea, including three who had arthritis, responded promptly and favorably to disulon^{46, 291} Neuritis was noted as a complication^{46, 479, 582} Sulfanilyl-sulfanilamide was considered more effective than dimethyl-sulfanilamide⁵⁸² Despite these claims, the percentage of cures (70 to 95) was about the same as has been reported for sulfanilamide

Fever Therapy Of Culp's 19 patients with gonorrheal arthritis (nine with acute, six with subacute and four with chronic), four became "well," six were "markedly improved" by fever therapy which was considered "efficacious but heroic" because of reactions These reactions consisted of heat stroke in three cases, convulsion in one, delirium in one, and death in one case Of Feiderber's 96 patients 70 per cent "improved" Of Trautman's 117 patients 87 per cent were "markedly improved or recovered"

Fever Therapy Plus Sulfanilamide for Gonorrhea and Its Complications For gonorrhea, or gonorrheal arthritis resistant to sulfanilamide, Mann gave sulfanilamide 100 grains daily for two days, then six hours of fever (106.5° F rectal) results in gonorrhea were good but "gonorrheal arthritis proved less responsive" [No details given—Ed] Fever therapy plus sulfanilamide cured 86 per cent of the patients of Belt and Folkenberg who had sulfanilamide-resistant gonorrhea [No details re arthritis—Ed] Patients received sulfanilamide, 80 grains daily for two days prior to the first fever treatment, then 20 grains one hour before each of three fever sessions (five hours at 106.7° F) given every other day

Other Remedies Culp reviewed results in the treatment of 200 cases of gonorrheal arthritis with numerous types of therapy Sulfanilamide, mercurochrome given intravenously and fever therapy gave best results Sulfanilamide and mercurochrome given intravenously seemed to be of equal value Fever therapy caused more severe reactions, involved greater risks and was "more heroic" than the other two methods

[It is interesting to note that results from meicrochrome given intravenously compared so favorably with those from sulfanilamide—Ed]

Autohemotherapy combined with short fever sessions was recommended for gonorrheal arthritis by Ishmael. Gonococcic vaccine was recommended by some ^{122, 542}

[It is hoped that this useless form of therapy (vaccines) will soon die a natural death—Ed]

TUBERCULOUS ARTHRITIS

Clinical Data Since bovine tuberculosis now affects only 0.4 per cent of cattle, tuberculosis in man now is due almost entirely to the human type of bacilli ²⁰. Clinical features of tuberculosis of spine, hip, and knee were reviewed ²⁰⁴

Diagnosis The importance of early, correct diagnosis of tuberculous arthritis was emphasized by Frupp. At first the disease may be extra-articular and articular symptoms may be absent. The importance of repeated roentgenograms and synovial biopsies in doubtful cases and the advantages of microscopic examination of tissue and guinea-pig inoculations from regional lymph nodes were discussed. Negative results were inconclusive. A positive Mantoux test per se has little value, but it may corroborate other findings. There is no infallible diagnostic method in early tuberculous arthritis.

Special Localizations Weight bearing joints are involved in about 95 per cent and those of the spinal column in 52 per cent of all cases of tuberculous arthritis ¹¹⁴

1 Spinal Column An excellent symposium on tuberculous spondylitis was reported in 11 papers cited briefly herein, the pathology, pathogenesis and medical and surgical treatment (with end results) were discussed. [As these cannot be reviewed adequately herein original references should be consulted—Ed] Pott's disease accounted for 698 deaths in the United States in 1937, that is, 1 per cent of all deaths from tuberculosis ¹⁶. Pott's disease must be regarded as a local manifestation of a general chronic tuberculous infection; its pathology was reviewed by Key ³²¹. Objectives of treatment should include relief of pain, healing of the spine, prevention or cure of deformity (compatible with healing), of complications and of relapses and prolongation of life ²¹⁴. Surgical fusion of the vertebrae is only an aid, and not in itself a cure for Pott's disease, prolonged general care is always advisable and surgical fusion should be postponed until forces of resistance become organized and until the lesion becomes stationary or starts to heal ^{16, 105, 390, 406}. Clinical features and results of surgical fusion in 1419 cases, tabulated from the symposium reports, appear in table 1.

Factors influencing end results included early treatment, severity of infection and the patient's resistance. Cleveland reported a mortality rate of 9.5 per cent among patients without active tuberculosis elsewhere than in the spinal column, and 54.5 per cent among those with active tuberculosis elsewhere. This indicates the desirability of controlling tuberculosis of lungs and other organs before attempting fusion operations.

TABLE I

Summary of Clinical Data and Results of Surgical Spine Fusion for Pott's Disease

	Authors					
	Swift	Cleveland	Meyerding	Chandler and Page	Adams	Harris and Coulthard
Cases	584	173	480	39	63	80
Follow-up, years	10+	5+	5+	5-10	5+	5+
Vertebrae affected		Chiefly lower thoracic and lumbar	Chiefly thoracic and lumbar	Low thoracic and lumbar chiefly	Low thoracic and lumbar	
Complications on admission, per cent of cases						
Abscess		68	52	69	64	90
Paraplegia		24	17.5	8	13	16
Active pulmonary tuberculosis				13	8	30
Tuberculosis of other organs					25	30
Per cent in various age groups at operation						
0-10	57	21	4	82	0-12	11
10-20	43	16	6	18	100	14
20-30		26	45			45
30-40		16	28			20
Over 40		21	17			11
Type of operation	Hibbs	Hibbs	Albee, Hibbs Osteoperiosteal graft	Hibbs	Hibbs Albee Laminectomy Osteoperiosteal graft	Bone grafts
Results per cent of cases "good" or "excellent"		54.2	64	74.4	60	58
Early	50					
Delayed	14					
0-10 years	72					
10+ years	53					
"Improved" or "uncertain"		19.2	11			18
"Poor" or "failure"	8	7.4	6	10.2		12
Relapse		4	3.8			10
Death	28	26.6	18	15.4	40	12
Cause of death per cent of cases						
Uncomplicated		9.5				
Postoperative shock or infection	5					8
Tuberculosis						
Pulmonary	13			17		4
Meningitis	18	54.5		50		4
Other organs	22					54
Miscellaneous	42			33		30

Swett and his colleagues found no statistical advantage in operative, compared to nonoperative, treatment as determined by incidence of healing. Mayer compared results obtained by 37 patients treated surgically and 29 comparable patients treated nonoperatively. If done during active tuberculosis, fusion does not alter the course of the tuberculous process, if done during the reparative stage, it strengthens a weak spinal column and thus is beneficial. Most statistics show lower mortality rates among patients who have been operated on compared to those not operated on. [Many patients are not treated surgically because of an extensive infection or serious complication making for a poor "surgical risk." Unless comparable cases are studied, comparative results mean little—Ed.] Surgical treatment was generally believed to be helpful, although good statistical proof is scarce.^{105, 214} Chief arguments for surgical treatment are reduction in time for healing,¹¹⁴ more certain healing²⁴⁴ and fewer relapses. According to most investigators, fusion operations give better results in children.^{114, 502} But Meyerding prefers con-

servative treatment for children and thinks results from fusion operations are better for adults

Healing rarely occurs in the presence of an abscess, according to Swett and his associates. Hence they and others^{114, 244} advised early aseptic evacuation of all abscesses. But Meyerding recommended that abscesses be left alone unless they are causing symptoms of pressure or absorption of bone.

2 Hips Tuberculous trochanteritis must be differentiated from tuberculosis of the hip proper²⁸⁶, radical excision, resection or thorough curettage gives superior results. Although the condition is serious and disabling, the prognosis is good.

3 Knees Arthrodeseis of knees for tuberculosis can be performed successfully on children as young as 27 years³²¹. Usually, two operations are needed, more time is required for ankylosis in younger children. In most cases there was no loss of growth, in others it was not more than $\frac{1}{2}$ inch.

4 Other Sites Wassersug described femoral trochanteric tuberculosis, in two cases peritrochanteric bursae alone were involved. A case of isolated tuberculosis of a vertebral spinous process was reported¹⁸.

OSTEITIS TUBERCULOSA MULTIPLEX CYSTICA

No reports on this disease appeared.

"TUBERCULOUS RHEUMATISM"

This questionable disease entity was not discussed.

PNEUMOCOCCAL ARTHRITIS

Pneumococcal arthritis complicates only about 0.1 per cent of cases of pneumonia and has almost disappeared since the introduction of chemotherapy³¹. Successful treatment with sulfapyridine in one case was reported²⁹⁸. [No cultures were made from the joint, there is doubt about the diagnosis—Ed.]

SYPHILITIC ARTHRITIS AND SYNOVITIS, CHARCOT (TABETIC) JOINTS

Syphilitic Arthritis The relationship of syphilis to chronic arthritis was studied by Kuhns and Feldman. Of 1,154 patients with chronic arthritis only 13 were found to have serologic reactions positive for syphilis. On none of the 13 could a diagnosis of syphilitic arthritis be made. They concluded that syphilis has no relationship to chronic arthritis other than as an occasional coincidental disease. Transient joint pains occur often in early syphilis. Effusions (synovitis) also may occur during the course of acquired or congenital syphilis^{128, 244}.

Charcot Joints This neuro-arthropathy affects from 6 to 10 per cent of tabetics. It may occur also in syringomyelia, injuries to cord, and leprosy. Soto-Hall and Haldeman analyzed 40 cases of tabes in which 65 joints were affected.

Average age of onset of articular symptoms was 45 to 50 years, extreme ages being 29 and 68 years. Fifty of the 65 involved joints were in lower extremities, only seven joints in upper extremities were affected. The spinal column was affected in seven cases, the sacro-iliac joints once. Trauma may explain this difference of incidence in joints of lower extremity and the rest of body. Onset of articular disease began after acute injury in almost 50 per cent of these cases. In 40 per cent involvement was bilateral. Neurologic data (Argyll Robertson pupils, absent knee jerks) were more often positive and helpful in diagnosis than were laboratory data.

Ten other cases of Charcot joints were reported^{128, 180, 188, 353}. One was a case of congenital syphilis with syringomyelic dissociation and arthropathy of the elbow joint¹⁸⁸. The early and progressive roentgenographic changes seen in the different joints were described⁴¹⁰.

Treatment is unsatisfactory. Antisyphilitic treatment should be given but does not often affect joints, the process therein may develop and progress to destruction, even while the syphilis is being vigorously treated. Supports and braces are useful to reduce trauma to joints. The knee is most suitable for surgical procedures (arthrodesis)³⁹¹.

BRUCELLOSIS UNDULANT (MALTA) FEVER

General reviews and discussions of public health aspects of this disease appeared^{58, 173, 284, 287, 405, 459, 460, 608}.

Symptoms Referable to Muscles and Joints Arthralgia, severe backache, neuralgia, "neuritis," myalgia, leg pains and generalized body aches are common during the acute and postfebrile periods^{275, 282, 351} but cases of significant arthritis are rare. Although arthralgia and myalgia are prominent symptoms, in about half of the cases of acute brucellosis, hydrarthrosis and transient periarticular swelling occur only occasionally, and permanent articular impairment is rare^{511, 512}. Cases of muscular and joint pains "resembling rheumatic fever" were again noted²⁸⁴. Among 70 cases of Greene, "rheumatism or arthritis" was the entrance-complaint only once, "symptoms of arthritis" [not defined—Ed] were noted in only seven. Orthopedic complications include pyogenic involvement of a single joint, serous polyarthritis, and osteomyelitis generally of lumbar vertebrae according to Steindler who noted a case of acute nonsuppurative arthritis. [Data on this case were very meager—Ed]. According to Harris "an important, and perhaps large percentage of cases of run-of-the-mill arthritis are caused by *Brucella* infection."

[With this we cannot agree. Harris gave no statistical proof. One of us, R. H. F., studied 25 cases of typical rheumatoid arthritis for evidence of brucellosis without success. Of 25 cases of rheumatism not typical of any common arthritis, in three active brucellosis was present and in six "possible brucellosis." It was concluded that rheumatic symptoms are common in brucellosis and temporary inflammation of joints may occur, but seldom if ever does brucellosis cause chronic, non-purulent inflammation of joints—Ed.]

Diagnosis Except for isolating *Brucella* organisms, there is no method by which the diagnosis can be proved. Skin and agglutination tests and opsonocytophagic studies should be done in suspected cases, results should be evaluated only with clinical findings^{55, 195, 226, 261, 267, 511, 512}. Chief sources of error and the inadequacies of

laboratory tests were emphasized again⁵¹¹ In many cases previous infection and active infection cannot be distinguished by laboratory tests^{39, 53, 64, 287} Skin reactions to *Brucella* nucleoprotein (brucellergen) and to heat-killed organisms occurred in essentially the same number of sensitized individuals³¹³ Foshay preferred brucellergen for intradermal tests Dustin and Weyler considered a febrile response (100° F or more) to the intramuscular injection of 0.5 cc of a solution of 2,500,000 bacteria [presumably *Brucella abortus*—Ed] of significance comparable to skin reactions [Critical comparison with results of other laboratory tests was not made—Ed] A modification of Huddleson's opsonocytophagic reaction was described

TREATMENT OF BRUCELLOSIS

Chemotherapy Except for the sulfonamide compounds, chemotherapy has been largely abandoned^{20, 220, 511} Additional reports of cases "successfully treated" by sulfanilamide appeared^{55, 108, 243, 283, 351, 418, 506} but failures were also recorded^{20, 283, 512, 530} Many believe sulfanilamide valuable chiefly in the acute stages^{20, 351} But Holland abandoned it and neoprontosil as valueless in acute cases of *Brucella melitensis* infection, his results with sulfapyridine were "spectacular" Generally, large doses of sulfanilamide (4 to 6 gm daily) were advised⁵⁰⁶, a few^{108, 283, 418} considered smaller doses (1.5 gm daily) preferable Relapses following treatment with sulfonamide compounds were frequent^{20, 275} The combined use of sulfonamide compounds and vaccine²⁸³ or fever therapy³⁶¹ was considered better than chemotherapy alone

In mice aldanil (sodium formaldehyde sulfoxylate derivative of sulfanilamide) and sulfanilamide gave the best therapeutic results in *Brucella abortus* infections, sulfapyridine was superior in *Brucella melitensis* infections, and sulfanilamide in *Brucella suis* infections³⁸² Sulfamethylthiazole was more effective than sulfanilamide in treatment of *Brucella* infection in mice⁴¹⁷ Toxic effects of sulfanilamide and sulfapyridine were noted⁴⁰³

[Earlier enthusiasm for the sulfonamides in the treatment of brucellosis has waned A definite evaluation of sulfonamide drugs on the basis of current reports is impossible Perhaps more effective sulfonamides may be developed—Ed]

Serums and Vaccines Good results were claimed for Foshay's serum^{20, 284} [It is still not available commercially—Ed] A method for the preparation and purification of antiserum was described²⁸⁸ "Immune transfusions" and convalescent serum were considered valuable^{275, 536} Specific vaccine therapy gave "best results" for some,²⁸⁴ and was considered "preferable,"²⁰ "unreliable,"²⁸² and valueless^{226, 351} by others

[The method of action is still unexplained on a sound immunologic basis—Ed]

Fever Therapy Febrile responses are desired, and were thought to be responsible for benefit from vaccine treatment^{20, 511} Simpson^{511, 512} reserved fever therapy for refractory cases

Other Treatment Ultrashort wave (6 meter) diathermy to "inaccessible foci" of (*Brucella*) infection such as gall-bladder and fallopian tubes was recommended by Harris [no details given—Ed]

[Obviously no "specific" or totally reliable treatment for brucellosis exists More study of therapy is needed—Ed]

TYPHOIDAL ARTHRITIS

No data were reported

MENINGOCOCCAL ARTHRITIS

In the British Expeditionary Force (1940) a mild epidemic of cerebrospinal fever occurred. Stott and Copeman noted 17 cases of chronic meningococcal septicemia without meningitis. Presenting symptoms frequently masqueraded as rheumatic fever or erythema nodosum. Present were fever, chills, headache, severe migratory joint and muscle pains. Joint effusions were not uncommon. Within a few days the characteristic rash occurred. Meningococci were found in cultures of the blood. Sulfapyridine promptly cured the disease. No suppurative meningococcal arthritis occurred.

SUPPURATIVE ARTHRITIS

General Comment Suppurative arthritis must be considered in the differential diagnosis of acute rheumatic fever and other acute articular disturbances.⁸⁵⁴ Study of the frequency of recurrence of infection after elective operations in cases of healed suppuration in joints was made by Davis.¹⁵⁰

Of Streptococcal Origin. A case of suppurative arthritis due to infection with Group B hemolytic streptococci (Lancefield) was reported by Rantz. This is the first case recorded in which Group B hemolytic streptococci have been recovered from suppurative arthritis of man. Group B organisms are more commonly associated with bovine mastitis and are only rarely pathogenic for humans.

Of Staphylococcal Origin Staphylococcal septicemia and septic arthritis of the knee were successfully treated in one case by the oral use of sulfapyridine, multiple aspirations and irrigations (Kendrick⁸¹⁶).

Treatment General principles were outlined^{88, 816, 819, 854}. A careful review of the recent changes in methods of treating suppurative arthritis and osteomyelitis was made by Beekman and Sullivan.

New methods of treatment are based on the fact that the bone or joint condition represents only a manifestation of a systemic condition involving a blood stream infection, hence surgical intervention should be secondary to therapy directed toward the general condition. No operative procedures should be done until the focus is reasonably well established as a bone abscess. Even then, the operation must involve a minimum of interference, yet secure drainage and relief of tension, preferably through packing of the wound in the soft parts with vaseline gauze (petrolatum) and instituting complete rest of the part by plaster encasement and infrequent dressing. Many fatalities result from too early operation, all fatalities are due to septicemia or pyemia and never to the bone lesion. In treating the general condition, whether the infection is due to hemolytic streptococci or to staphylococci must be determined, for these two organisms give rise to two distinct disease processes requiring entirely different therapy.

The new method of procedure recommended is as follows. On admission to hospital a tentative diagnosis is made and the patient's general physical condition is built up through the administration of intravenous clyses and blood transfusions when indicated. Cultures of blood and synovial exudates are made to determine the bacterial invader. The involved limb is completely immobilized in splints or by a plaster casement. A distended joint is always emptied of its effusion by aspiration before the

limb is immobilized When the fluid equilibrium of the body is established (within 6 to 18 hours) the question of draining the lesion may be considered In the presence of a well formed abscess in soft parts or a pyarthrosis with thick pus, operation is not delayed further But if a thin exudate has been obtained through aspiration, or the invading organisms are hemolytic streptococci, operation is postponed In some cases an active focus can be cured simply through immobilization of the part, in others the inflammation becomes localized by rest, and the establishment of drainage at a later date is easier and more efficient Sulfanilamide should be given in those cases in which hemolytic streptococci are shown to be the causative agent

The local use of sulfanilamide in cases of suppurative arthritis (and war wounds involving joints) was advised by Key, Frankel and Burford Joint tissues tolerate the drug well but sulfanilamide should be sterilized (by autoclaving the dried powder) before being placed in clean wounds Sulfanilamide powder slightly inhibits primary healing of wounds but not to such a degree as to contraindicate its use in clean operative wounds when infection is feared It can be used repeatedly in open infected wounds and does not interfere seriously with the healing of such wounds

[These conclusions were based not only on clinical experience but on animal experimentation the treatment of experimental fractures and of experimental wounds in joints and muscles—Ed]

Following arthroplasty in two cases of ankylosis of knees from acute pyogenic arthritis Campbell⁸² interposed a vitallium plate the amount of motion obtained was disappointingly small

RARER FORMS OF SPECIFIC ARTHRITIS

No new data were reported on the arthritis of scarlet fever, of ulcerative colitis, of bacillary dysentery or of lymphogranuloma venereum

Haverhill Fever (Rat-Bite Fever) An attempt to harmonize different points of view as to the etiology of rat-bite fever was made by Allbritten, Sheely and Jeffers who tried to distinguish between rat-bite fever due to infection with *Spirillum minus* (Sodoku or Japanese rat-bite fever) and the type caused by *Streptobacillus moniliformis* (Haverhill fever) They stated that arthritis occurs only rarely in the spirillum variety

[Two of us, W B and M H D, are unable to subscribe to the clinical distinction set forth in this article They are of the opinion⁷ that the evidence incriminating *Spirillum minus* as an etiologic agent in rat-bite fever rests on insecure grounds—Ed]

The relationship between pleuropneumonia-like organisms and *Streptobacillus moniliformis* was considered^{180, 329} An unusual case of arthritis caused by a "spirochete" was reported⁵⁹⁴ The spirochete was considered unique, unlike any previously described Later the same type of spirochete was recovered from the blood of another patient with acute nonsuppurative arthritis of a hip the patient had been bitten by a rat a month previously

[Although there was no history of a rat bite in the first case, from the microphotographs and description this case might well have been due to *Streptobacillus moniliformis*—Ed]

Arthritis with Coccidiosis Coccidioid infection has long been an important public health problem in the San Joaquin Valley. It is the cause of "San Joaquin Valley fever," "desert fever" or "desert rheumatism." Symptoms of the acute form are an influenza-like onset, malaise, headache, general aches and pains in thorax or elsewhere, fever, generally bronchitis, and the appearance two to 18 days after the onset of the disease, of erythema nodosum or erythema multiforme. Smith made an exhaustive epidemiologic study in 432 cases of acute coccidioidomycosis with erythema nodosum; all patients recovered without sequelae.

Points stressed were the difficulty of diagnosis, incubation period of one to three weeks after exposure to the spores, sensitivity to coccidioidin, a product of the causative fungus, *Coccidioides immitis*, to which sensitivity develops in from two to 17 days after the onset of symptoms, generally in the second week of illness, appearance of erythema nodosum concomitant with the development of freshly acquired allergy, contraction of the disease by inhalation of chlamydospores rather than by contact, the relationship of the incidence of the disease to climate and agricultural activities, the peak of the disease being in dusty fall and its ebb, in wet winter, and the high incidence among newcomers to the valley. Smith noted that since erythema nodosum develops in not more than 5 per cent of the cases of infection with *Coccidioides*, the series reported represents between 8,000 and 10,000 attacks of coccidioidomycosis.

[Smith stated that the skin lesions are often associated with "arthritis" (not defined). None of his patients had coccidioid granuloma. This rarely develops after "San Joaquin fever," according to Smith. White females seemed to be especially sensitive to San Joaquin fever, whereas coccidioid granuloma is prevalent among dark skinned males. Although Smith considered coccidioid granuloma a rare sequela of San Joaquin fever, a San Joaquin Valley worker who had previously had "Valley fever" recently came to one of us, P. S. H., with chronic destructive arthritis of both ankles which was proved by biopsy to be due to coccidioid granuloma. Coccidioidomycosis has now assumed added importance because of the location of an air training center in the San Joaquin Valley. It is being studied intensively by the public health authorities.—Ed.]

Rheumatic Sequelae of Rubella (Measles) During an epidemic of measles in the British Expeditionary Force in France, Bennett and Copeman noted the occurrence of "rheumatic symptoms," which varied from transient joint and muscle pains (15 per cent) or articular effusions, to a condition "indistinguishable from rheumatic fever."

[Is it possible that the latter cases were secondary to hemolytic streptococcal throat infections rather than to measles?—Ed.]

RHEUMATIC FEVER

Several reviews concerned the clinical features of rheumatic carditis,³⁰⁵ epidemiology,^{247, 252, 255, 441, 470} theories of etiology,^{299, 500} pathology,¹⁵⁷ therapy,³⁹⁶ and public health aspects⁵⁶¹ of rheumatic fever.

A translation of the 1736 edition of *De Rheumatismo* by Balonius, 1538–1616,⁴⁸³ and a note on the history of the disease in Great Britain⁴⁷⁸ will appeal to those interested in medical history.

Incidence Many good articles on the incidence of rheumatic fever appeared during 1940, including those by Hedley who estimated that rheumatic fever in its

various forms, including chorea and inactive rheumatic carditis with and without superimposed bacterial endocarditis, was responsible for 0.70 per cent of all admissions to Philadelphia hospitals, 1.56 per cent of all admissions to children's hospitals, 2.4 per cent of medical admissions to general hospitals, and 5.8 per cent of medical admissions to children's hospitals. It accounted for 50,000 patient-days annually in Philadelphia hospitals and cost these institutions more than \$272,000 a year, exclusive of physicians' services. Rheumatic heart disease, including cases of superimposed bacterial endocarditis, caused 0.10 per cent of all hospital deaths in that city [Hedley's 1940 papers have been summarized in a monograph²⁵²—Ed]. In New Haven, Farquhar and Paul found that active rheumatic manifestations were responsible for 1.2 per cent of medical admissions to general hospitals and inactive rheumatic heart disease another 1.5 per cent. In Adelaide, Australia,⁴⁷⁰ acute rheumatism accounted for 1.8 per cent of all admissions to a children's hospital and for from 0.26 to 0.33 per cent to hospitals for adults. Swift^{570, 581} estimated that in New York State in 1938 more than 5,400 deaths were due to rheumatic heart disease. Contrary to common opinion, rheumatic heart disease is an important cause of death in the age groups 40 to 60 years as well as of younger persons. Swift estimated that there were about 460,000 patients in the United States who had rheumatic cardiac disease, this is a "conservative figure." The importance of rheumatic fever and rheumatic heart disease as causes of death is indicated by his calculation that they caused 147 deaths per 100,000 in New York City in 1938, compared with the following rates for other diseases: whooping cough 1.4, epidemic meningitis 0.7, measles 0.56, poliomyelitis 0.05. According to Clarke,¹¹² 0.54 per cent of the national school population of Eire has rheumatic heart disease, and 1.2 per cent of the school children in Dublin City "are probably rheumatic." Of Clawson's cases of noncongenital heart disease in which necropsy was performed, 18.7 per cent were of rheumatic origin.

Predisposing Factors Governing Incidence 1 Geography and Climate

The relative infrequency of rheumatic fever and the rarity of typical polyarthritis in southern as compared with northern states were mentioned again, no new data were given^{24, 271, 581}. The contention that the disease does not exist in the tropics was refuted again in reports from southern India^{348, 500, 599}.

The rôle of meteorologic factors received more attention than in recent years. In Iowa rheumatic fever was uncommon during several dry, mild winters, but returned to its usual frequency the following wet, cold winter⁴⁶². Hedley²⁵⁰ believed the prolongation of winter's cold might be related to the increased incidence of rheumatic fever in the spring, but, considering the possible rôle of lack of sunshine, he found no indication that the amount of precipitation affected the rate of rheumatic admissions to Philadelphia hospitals. No certain relationship was found between the wetness of the season and the rate of admission to hospitals of patients with rheumatic fever in southern Australia⁴⁷⁰. The presence of creeks and rivers also played no etiologic rôle,^{251, 470} but sections where dry heat prevailed had less of the disease than those with combined dampness, high rainfall and relatively cold temperature⁴⁷⁰. When this latter combination of conditions prevailed the disease was most prevalent in Eire also¹¹². In an important study of environmental factors in New Haven, Paul⁴⁴² found the highest incidence in the two wettest districts investigated.

2 Season The usual seasonal incidence in the United States, highest in late winter and spring and lowest in fall and late summer, was confirmed^{250, 584, 581}.

In southern Australia ⁴⁷⁰ the incidence was high from late autumn to early spring (peak in midwinter) and lowest in late spring and early summer, winter there corresponds with the summer months in the United States. There was much less seasonal fluctuation for chorea than for polyarthritis and carditis ^{112, 250}

3 Social and Hygienic Factors The well known tendency for rheumatic fever to occur predominantly among the poor was again noted ^{112, 250, 561}

Paul found no consistent increase in incidence in the poorest districts studied, but did find a fairly low prevalence in the single wealthiest district. In Australia, ⁴⁷⁰ density of population exerted a greater influence than poverty per se on the incidence of rheumatic fever, but the disease was relatively more severe in rural areas

4 Family, Heredity, and Constitution The increasing importance attributed to heredity in rheumatic fever in recent years was reflected in the literature

The familial incidence was 24 per cent in one group of rheumatic patients, ⁴⁶² 30 per cent in another ⁴⁷⁰ and 8 per cent among nonrheumatic controls. Perry ⁴⁵⁰ studied two pairs of apparently identical twins, both of one pair but only one of the other pair developed rheumatic fever. Perry concluded that although heredity is of considerable importance, another factor, probably infection, plays an equally, if not more, important rôle. Gauld and Read ^{205, 467} studied the incidence of the disease in families prior and subsequent to exposure of any member of the household to rheumatic fever. Their data supported the hypothesis that in the etiology of rheumatic fever both hereditary and environmental factors are involved and that the latter must act over a long period.

Dark eyes and hair were found more commonly in rheumatic children than in a control group ^{277, 470}. The distribution of the four main blood groups in rheumatic subjects was the same as in the general population ³⁸⁹

5 Sex The hospital admission rate for rheumatic fever was essentially the same for males and females, in Philadelphia ²⁴⁸ and in Adelaide, Australia ⁴⁷⁰. In the latter city chorea was slightly more common among females, in Philadelphia it was twice as common among females as among males. In Dublin 60.6 per cent of rheumatic subjects studied were females, 39.4 per cent were males ¹¹². Clawson's necropsy records indicate that rheumatic heart disease is about equally common among males and females, but the latter die earlier because they have more serious cardiac lesions.

6 Age In Dublin ¹¹² the average age at onset was reported to be 7.5 years for polyarthritis, 9.7 years for chorea, the peak incidence was about 9 years of age for polyarthritis and 10 for chorea. Both Sangster ⁴⁷⁰ and Hedley ²⁴⁸ found that the greatest number of first attacks occurred between the ages of 5 and 14 years. According to Gauld and Read periods of increased incidence are from 5 to 14 and from 25 to 34 years. Hedley ²⁴⁸ found that rheumatic fever in more than 75 per cent of cases, chorea in more than 98 per cent, rheumatic heart disease in nearly 70 per cent, begin before the age of 20 years and more than 30 per cent of deaths from rheumatic heart disease occur before this age.

7 Race The incidence of rheumatic fever among American negroes is low ^{247, 554}, their unfavorable economic circumstances makes this the more striking. Natives of Uganda ⁵⁰⁹ and of Australia ⁴⁷⁰ were thought to have no racial immunity to the disease.

8 Trauma In from 4 to 96 hours after trauma to certain joints of 12 patients, acute rheumatic episodes appeared therein ⁴⁷⁰. The greater work of the left side of the heart is usually thought to be the reason for the predominance of rheumatic lesions

on that side, Coburn suggested that the difference in the oxygen tension on the two sides may be the cause

General Symptomatology Certain clinical statistics were recorded

Acute rheumatism (including carditis) was the cause of admission to hospitals of 64.5 per cent of 450 rheumatic children, chorea, of 29.3 per cent, the two combined of 62 per cent.⁴⁷⁰ On services for adults comparable figures were 83.8 per cent, 14.9 per cent, and 1.3 per cent. The distribution of manifestations in Clarke's 545 cases in Eire was as follows: rheumatic fever 42.7 per cent, insidious carditis 13.5 per cent, polyarthritis 13.5 per cent, postscarlatinal arthritis, 1.5 per cent, postscarlatinal carditis 0.5 per cent, chorea 28.0 per cent and rheumatic erythema nodosum 0.2 per cent. Rheumatic carditis occurred without a history of previous rheumatic manifestations in from 42 to 58 per cent of cases studied.^{357, 462, 490}

PATHOLOGY OF RHEUMATIC FEVER GENERAL CONSIDERATIONS AND SPECIAL CLINICOPATHOLOGIC DATA

An excellent account of morphologic changes in various organs was given by de la Chapelle. Cardiac lesions in rabbits which easily could have been mistaken for Aschoff bodies were noted by Loewe and Lenke. Coburn agreed with Klinge that "the apparent damage to collagen fibrils" in rheumatic lesions "really consists in an alteration of the mucoprotein ground substance."

Cardiovascular System In keeping with their great importance, cardiac lesions received much attention, but little new information was reported.

In two series of necropsies^{113, 357} the relative frequency of involvement of the various valves was given. The so-called Monckeberg sclerosis of the aortic valve was considered rheumatic in origin.^{113, 306} Contrary to the generally accepted view, another group of workers³²⁸ considered proliferative lesions of the heart, as exemplified by the Aschoff body, to indicate that rheumatic activity has subsided. [One of us, C. M., believes that this interpretation is untenable on clinical grounds and is unsound pathologically—Ed.] A simple "two step, cardiac function test" was used to determine when rheumatic carditis has reached an inactive stage.³⁴⁸ Roth⁴⁸⁰ found auricular fibrillation rare in young adults except as a terminal event but present in 20 to 25 per cent of those past 40 years of age. Papers appeared on the clinical features, course, and physiologic abnormalities of rheumatic tricuspid disease¹⁸ and of pure mitral stenosis,⁵⁸⁵ also on the clinical, pathologic and roentgenologic features of valvular calcifications in rheumatic and nonrheumatic heart disease.^{177, 178}

Joints Roth⁴⁸⁰ believes that carditis does not occur without arthritis in children much oftener than in adults. Brief notes on the character of synovial fluid in six cases were given.⁴⁷⁰ Features of rheumatic polyarthritis were discussed.^{290, 348, 470, 478, 480, 548, 555, 599, 611} No new information was given.

Nodules An excellent study of subcutaneous nodules of rheumatic fever and rheumatoid arthritis was reported by Bennett, Zeller and Bauer according to whom nodules in the two diseases, although similar, are sufficiently different to suggest that the two diseases may be caused by different agents. Subcutaneous nodules were present in 4.4 per cent of 450 children and in 0.6 per cent of 390 adults with rheumatic fever in southern Australia.⁴⁷⁰ They

occurred in 58 per cent of children with polyarthritis and in 07 per cent of those with chorea

Lungs and Pleura The question of the frequency and, indeed, of the existence of "rheumatic pneumonia" remains unsolved

De la Chapelle described pleural lesions but had not encountered a satisfactory example of rheumatic pneumonia The absence of Ewart's sign in nonrheumatic pericarditis suggested to Gevalt and Levine that its presence in rheumatic pericarditis and pleuritis is due to a coexisting rheumatic pneumonitis But Robbins and Durante warned of the danger of misinterpreting Ewart's sign to mean pneumonia instead of pericarditis

Skin In 53 per cent of 450 rheumatic children skin lesions were noted during the active infection erythema marginatum, erythema multiforme, or an urticaria-like rash⁴⁷⁰

Nervous System The features of chorea were described^{218, 500}

In 614 per cent of 223 cases choreic movements were bilateral, in 26 per cent predominantly or exclusively right-sided and in only 126 per cent left-sided⁴⁷⁰ Bruetsch saw four more cases of dementia praecox, rheumatic heart disease and organic changes in the brain, he contended that rheumatic fever was a cause of dementia praecox in 9 per cent of the cases of dementia praecox he has examined pathologically

LABORATORY DATA IN RHEUMATIC FEVER

Electrocardiogram Electrocardiograms of 150 normal girls were studied by Reyersbach and Kuttner In 5 per cent the auriculoventricular conduction time was abnormally prolonged, possibly because of increased vagal activity It was concluded that prolongation of the P-R interval is not in itself a reliable index of myocardial involvement

Sedimentation Rate of Erythrocytes This was again considered the most important single laboratory test of rheumatic activity^{87, 385, 402, 555, 584, 587}

Hemoglobin In the presence of a rapid sedimentation rate, Wallgren considered a decreasing level of hemoglobin evidence of persisting serious activity but a rising level of hemoglobin favorable

Blood Chemistry Phosphorus in the blood of rheumatic children was found to be relatively low¹⁷⁰

Weltmann Reaction In chorea this test gave usually normal or increased values, in polyarthritis and carditis values were low but returned to normal earlier than the sedimentation rate³²⁸

RELATIONSHIP OF RHEUMATIC FEVER TO OTHER DISEASES

Rheumatoid Arthritis As has been mentioned, histologic differences in the subcutaneous nodules of rheumatic fever and rheumatoid arthritis suggested to some⁴² that the two diseases are of different etiology

Subacute Bacterial Endocarditis The importance of rheumatic heart disease in preparing the way for subsequent bacterial endocarditis was pointed out^{247, 357} Subacute bacterial endocarditis in 645 per cent of Hedley's²⁴⁸ 324 cases was regarded as superimposed on rheumatic heart disease

Sydenham's Chorea Chorea generally was accepted as a manifestation of rheumatic fever^{70, 217, 218, 219, 290, 395, 403, 500} Struthers stated that rheumatic heart disease was likely to develop in cases of chorea only when polyarthritides also was present, but Hedley²⁴⁷ found that rheumatic heart disease developed in 46.5 per cent of 4,616 cases of chorea and that even in 28.8 per cent of 526 cases of so-called pure chorea, rheumatic heart disease was diagnosed.

Erythema Nodosum It is believed that certain cases of erythema nodosum are of rheumatic origin and others not^{113, 470}

DIFFERENTIAL DIAGNOSIS IN RHEUMATIC FEVER

Discussed were the differentiation of rheumatic and nonrheumatic "growing pains"^{24, 290, 383} and rheumatic and syphilitic heart disease^{90, 404} Clawson found pericarditis so frequently at necropsy in cases of subacute bacterial endocarditis that he argued that the presence of pericarditis cannot be used clinically in differentiating between that disease and rheumatic carditis [We cannot agree with this clinical conclusion—Ed] The danger of mistaking pericarditis with effusion for lobar pneumonia was emphasized⁴⁷² Other diagnostic difficulties were discussed^{84, 509}

PROGNOSIS AND END RESULTS OF RHEUMATIC FEVER

The immediate mortality in the first attack of rheumatic fever is low, especially among adults, this was again shown by an analysis of results of the first attacks on 405 children and 309 patients more than 12 years of age⁴⁷⁰

The immediate mortality rate was 4.69 per cent for the children, only 0.32 per cent for the adults. For the total of 714 patients the immediate mortality rate was 2.8 per cent. Hedley²⁴⁹ estimated that 3.5 to 4.5 per cent of first attacks terminated fatally. But Gibson²¹³ took a more gloomy view, in his 146 fatal juvenile cases, death occurred within one month of the onset in five, within four months in 19, and within one year in 20 more. To him nodules and pericarditis were of serious prognostic significance, chorea and rheumatic erythemas indicated relatively mild infection. In contrast Struthers regarded erythemas and epistaxis as of serious import. Many believe that the older the child at the initial rheumatic attack, the less likely is carditis to result, but others⁵⁵⁴ found no indication that children whose first attack was in early childhood died sooner thereafter than those whose first attack came later. As between onset during childhood and adult life, there seems to be no doubt that the prognosis is distinctly better in the latter^{395, 470}

Death and the onset of heart failure in cases of old rheumatic heart disease usually are due to a recrudescence of rheumatic activity, this is especially true of children and young adults^{213, 249}. Thus it is important to recognize the signs and symptoms of carditis and of rheumatic activity in general. These were reviewed^{373, 395, 396, 543, 555}. The relative seriousness of aortic and mitral valvular lesions remains debatable^{113, 480, 585}

The serious ultimate prognosis was stressed. In follow-up studies of large groups of rheumatic children mortality rates of 15 to 30 per cent were recorded over periods of 10 to 18 years^{385, 554}. Among Hedley's²⁴⁹ 542 fatal cases, death from the primary rheumatic manifestation resulted in less than one year in 13.5 per cent, in less than five years in 32 per cent, in less than 10 years in more than 48 per cent. Although the outlook is serious once rheumatic heart disease has developed, the heart

does not always receive significant injury Thus, of Gibson's 1,487 patients with rheumatic fever or chorea, 42 per cent escaped evident heart disease In a study ⁴⁷⁰ of 523 first attacks, 66 per cent of the patients at the time of dismissal were thought to be without cardiac damage, as were 50 per cent of the 175 patients of Brown and Wolff followed for an average of seven years

Pregnancy in Rheumatic Heart Disease Data on maternal and fetal mortality rates and on various clinical features were given ^{109, 221, 249, 357, 554} The maternal mortality rate ranged from 22 to 181 per cent Pregnancy seems to protect rheumatic subjects against recrudescences of rheumatic activity after hemolytic streptococcal infections ¹¹⁵

[This is interesting, especially in view of the ameliorating effect of pregnancy on rheumatoid arthritis—Ed]

Rheumatic Fever and Jaundice Three patients with rheumatic fever had jaundice, two may have been benefited by the jaundice ²⁵⁶

ETIOLOGY AND PATHOGENESIS OF RHEUMATIC FEVER

Factor of Infection Infections of the upper respiratory tract preceded 34.2 to 86 per cent of rheumatic attacks ^{112, 299, 470} Jones and Mote found infections of the respiratory tract preceding 58 per cent of first attacks and 67 per cent of recurrent attacks of rheumatic fever In most of the cases without clinical evidence of respiratory infections there was serologic evidence suggesting recent infection with hemolytic streptococci Suppurative and highly invasive infections are rarely followed by rheumatic recrudescences, according to Coburn

1 Skin Tests Contrary to most earlier reports, Jones ²⁹⁹ stated that reactions to intradermal injections of streptococcic products were no greater in rheumatic subjects than in control groups if the opportunity of streptococcal infections was similar Green ²²⁴ noted dermal reactions in a normal subject tested with synovial fluid from three patients with rheumatic polyarthritis, the reaction could be "neutralized" by mixing serum from convalescent rheumatic patients with the fluid

2 Antifibrinolysins Boisvert noted that antifibrinolysin titers of rheumatic children usually remained high longer than those of most nonrheumatic children suffering from simple hemolytic streptococcal infections

3 Antistreptolysins According to Coburn, in cases of infections with hemolytic streptococci without subsequent rheumatic fever, the antistreptolysin titer rises no later than two weeks after the initial infection, but in cases of rheumatic fever titers rise in the third week and remain high as long as the disease remains active Bunim and McEwen noted that titers tended to be normal in inactive rheumatic heart disease but high in the active manifestations, including chorea There was no apparent relationship between the height of the titer and the severity of the disease

All previous studies on antistreptolysin in rheumatic fever, including those just mentioned, dealt with so-called antistreptolysin O Todd, Coburn, and Hill studied another variety, antistreptolysin S This antibody increases after hemolytic streptococcal infections as does the other, but, in contrast, it tends to be lower during bouts of rheumatic fever, thus its behavior differs notably from that of the antistreptolysin O titer

4 Complement Fixation Tests From liver and spleen of a rheumatic patient Coburn prepared an antigen which fixed complement in the presence of fresh rheumatic fever serum

5 Interpretation The obvious interpretation of these data is that hemolytic streptococci bear an important etiologic relationship to rheumatic fever ^{100, 170, 352, 460} According to Coburn heredity and environment combine to produce persons who do not handle respiratory infections with hemolytic streptococci in a normal manner. Their immune response to the primary infection is inadequate with the result that the cells of the reticulo-endothelial system become sensitized. Subsequent contact of antigen and antibody within the sensitized cells gives rise to an abnormal reaction leading to the characteristic inflammation of rheumatic fever.

[This stimulating paper deserves the attention of all students of the disease—Ed.]

6 Culture of Synovial Fluid From three of six specimens of synovial fluid a gram-positive, spore-bearing bacillus was isolated ¹⁷⁰ No etiologic significance was attached to it.

Virus Theory Inoculation of fluids from four joints and of suspensions made from two subcutaneous nodules into monkeys gave negative results ⁴⁷⁰ Spinal fluid from six choreic children was inoculated intracerebrally into rabbits by Loewe and Lenke. In some of the rabbits cardiac lesions were found which closely resembled those of rheumatic fever, but they were also found in control animals, hence they had no etiologic relationship to rheumatic fever. Eagles and Bradley retracted their previous statement that so-called elementary bodies found by them in rheumatic exudates might possibly be of etiologic significance. Swift,⁵⁸⁰ Sabin and Johnson found no pleuropneumonia organisms in rheumatic patients and concluded that these agents are not concerned in the disease. A virus was isolated from human rheumatic material by Jones ²⁹⁹ but it was apparently that of influenza, and was unrelated to rheumatic fever.

Factor of Vitamin Deficiency Monkeys were rendered scorbutic and then given intratracheal injections of hemolytic streptococci, one strain of which was of monkey origin. Results were negative ⁴⁷⁰ Although vitamin C deficiency is present in rheumatic fever, feeding adequate amounts of the vitamin will not prevent the disease ³⁰³ There is no proof that vitamin C deficiency is more deleterious in rheumatic fever than in any other infectious process ²⁹⁹

Conclusions on Etiology The reports of 1940 indicate that the promising work of the past few years on a possible virus etiology of rheumatic fever has led to disappointing results. The importance of infection with Group A hemolytic streptococci becomes more and more apparent, but whether these bacteria are the primary, or merely an important contributing, cause still has not been proved. Why rheumatic attacks develop after such infections in some cases and do not in others remains a vexing question. That heredity and environmental factors each are concerned grows increasingly clear. It should be noted that bacterial hypersensitivity again was suggested as playing a rôle by a new and authoritative voice (Coburn).

TREATMENT OF RHEUMATIC FEVER

General Remarks The treatment of all aspects of rheumatic fever was discussed ^{49, 323, 393, 396, 560, 571, 611}

Rest The extreme importance of rest was again stressed ^{273, 323, 393, 564, 571, 584, 611} Rest probably aids, in part, by diminishing tachycardia, thus

lessening the cardiac load³⁶⁰ Home occupational therapy was' considered valuable³⁸²

Salicylates If ordinary doses of 60 to 150 grains daily do not relieve polyarthritis, the amount should be increased to 200 or more, according to Marquis who gave up to 390 grains daily for short periods Salicylates are of great value in combating polyarthritis, fever and toxic manifestations of rheumatic fever, but they do not affect the fundamental course of the disease^{49, 56, 87, 396, 584, 611} A new and (if confirmed) important use of salicylates was reported by Boas and Ellenberg who obtained dramatic diminution of the effusion in 12 cases of pericarditis with effusion, myocarditis and endocarditis were unaffected

Sulfanilamide Additional reports^{280, 387} of the ineffectiveness of sulfanilamide in the treatment of rheumatic fever were made

[For its prophylactic use, see later —Ed]

Removal of Foci of Infection Upheld was the opinion that tonsillectomy is of minor, if any, importance in the treatment and prevention of rheumatic fever, the decision to perform the operation must be made in each case on the basis of the laryngologic indications^{101, 112, 286, 357, 383, 393, 402, 527, 555} Gingivitis or infected teeth play no evident rôle⁴⁰²

Vaccines and Serums Treatment with vaccines and serums has had little support in recent years but several reports during 1940 advocated their use

Cecil suggested that "streptococcus vaccines" may have prophylactic value if given yearly Wasson and Brown reported a much lower incidence of rheumatic exacerbations among patients given a broth filtrate of hemolytic streptococci than among controls

[This is contrary to previous results with vaccines —Ed]

To 15 patients with acute rheumatic fever Green and his colleagues²²⁵ gave serum from convalescent rheumatic patients nine were "benefited"

[This work needs confirmation, a number of unpublished trials of convalescent serum in rheumatic fever have given negative results —Ed]

Diet and Vitamins Vitamin C supplements have no curative or prophylactic effect in this disease, even so it may be important to correct the low blood vitamin C levels usually present^{708, 771} Kuttner found no decrease of upper respiratory infections in a group of rheumatic children fed large doses of vitamins A, B, C, and D, as compared with a control group not receiving the vitamin supplements three children experienced rheumatic attacks while taking the vitamins

Treatment of Chorea Fever therapy was recommended for severe chorea^{185, 263, 271, 550, 611} (It was valueless in 11 cases of rheumatic carditis treated by Heymann and Enright) Hughes warned of the dangers of nirvanol In five cases Hollander used intramuscular injections of lipoids extracted from ox brain the chorea cleared in six to eight days

[The author's explanation of the possible mechanism involved is not convincing but the method deserves investigation —Ed]

Institutional Care and Climate It was Swift's⁵⁰¹ "firm conviction" that "the average child in the subacute and chronic stages of rheumatic activity would be best treated in an institution where the special indications imposed by his disease can be adequately met"

Swift⁵⁰⁰ summarized these indications thus "To build up the patient's resistance against infection, to provide prolonged rest and thus reduce to the lowest possible level the damage to inflamed organs such as heart and blood vessels, to regulate exercise carefully so that a diseased organ may be slowly restored to its most effective physiological capacity, to provide suitable education in a psychologically proper atmosphere" A convalescent hospital in Sydney, Australia, was described²⁹⁰ In reviewing 15 years' experience at the Children's Heart Hospital of Philadelphia, Stroud and Twaddle did not find that prolonged hospitalization materially decreased the death rate nor increased the number of patients able to lead active lives in later years

No new data on climatotherapy were given^{200, 300, 501}

Treatment of Pregnant Rheumatic Cardiacs Special procedures used on two large obstetrical services were outlined^{100, 221}

PREVENTION OF RHEUMATIC FEVER

Prophylactic Value of Sulfanilamide The prophylactic value of sulfanilamide in rheumatic fever was reaffirmed by Coburn and Moore who brought their experience with it up to date rheumatic exacerbations developed in only one of 184 children given prophylactic doses of sulfanilamide as compared with their occurrence in 35 per cent among their children not so treated The drug was given in doses of 2 to 3 gm daily throughout the school year—sufficient to maintain blood levels of 4 to 5 mg per cent Toxic symptoms appeared in about 10 per cent of cases But some children, given sulfanilamide during convalescence from recent rheumatic attacks, developed recrudescences

Public Health Aspects Growing interest of public health departments in rheumatic fever was illustrated in the decision of the Central Board of Health of South Australia to conduct the valuable epidemiologic survey⁴⁷⁰ frequently referred to herein Rheumatic fever, chorea, and cardiac disease cause twice as many deaths among Australian children 10 to 15 years old as tuberculosis does Clarke¹¹² described efforts made in Dublin to meet the problem American needs were outlined by Swift^{500, 501} Based on an average rest in bed of six months for each patient and the experience in London, New York City would require about 1,750 beds for the care of rheumatic patients, actually there are only 300 to 400

CHRONIC ARTHRITIS THE TWO COMMON TYPES

In previous Reviews we have used the terms "atrophic" and "hypertrophic arthritis," terms used by the American Rheumatism Association To foster closer relationships with the rest of the English speaking world the Association recently adapted as preferred terms "rheumatoid (synonymous with chronic infectious, atrophic or proliferative) arthritis" and

"osteo-arthritis or degenerative joint disease (synonymous with hypertrophic or senescent arthritis) "

RHEUMATOID (CHRONIC INFECTIOUS, ATROPHIC, PROLIFERATIVE) ARTHRITIS

Influence of Heredity on Incidence In an Italian series the familial incidence of rheumatoid arthritis was about 30 per cent, affected were two boys and two girls in one of the families studied⁴⁶⁴ Concerning this factor Horder²⁸⁰ wrote "Obviously we cannot take measures to cure our ancestors But [by eliminating other predisposing factors] we can use diligence to see that our posterity has less cause to reproach us "

Clinical Data The various stages of the disease were described, also the minimal requirements for a diagnosis of rheumatoid arthritis^{102, 258, 259} and the differentiation of early rheumatoid arthritis from periarticular fibrositis⁵¹⁶ Projection of articular pain was discussed by Werndorff As a rule pain in joints is not projected, an exception is the extension of pain from arthritic hips to sciatic region, groin or knees Pain in the knees in coxitis is caused by pressure granulation tissue growing in the acetabular fossa as a result of synovial involvement presses on the obturator nerve

[This explanation is not wholly satisfactory Pain may be referred to knees from osteo-arthritic hips in which cases significant synovial involvement does not occur—Ed]

RHEUMATOID ARTHRITIS SPECIAL CLINICAL FEATURES

Effect of Hepatitis and Jaundice Usually considered an enemy to man's well being, hepatitis with jaundice may be distinctly advantageous to patients with rheumatoid arthritis who, with the onset of significant jaundice, may suddenly lose for a time all symptoms of active disease

Between 1933 and 1939 this phenomenon was noted 72 times in 45 cases by Hench, in 27 cases by others²⁵⁶ "Gold jaundice" from chrysotherapy may or may not provoke the phenomenon⁶ A patient given injections of sanochrysin by Cecil¹⁰² had no notable relief until toxic hepatitis and jaundice suddenly developed presumably from gold "Within a week or so after the onset of jaundice, swelling and pain disappeared entirely from the joints and there was complete restoration of function" This remission lasted more than three months Recently cases have been noted in which jaundice apparently induced temporary but impressive remissions from migraine, ragweed hay fever and egg sensitivity Discussing these probably related phenomena Hench raised certain questions Are hepatitis and jaundice anti-allergic? Is rheumatoid arthritis caused by an unknown type of hypohepatia or hyperhepatia which becomes temporarily corrected incident to hepatitis of the proper degree and type? The phenomenon proves that rheumatoid arthritis is not inherently irreversible, obviously the body of the arthritic patient, if properly stimulated, can correct quickly and effectively the disturbed physiology underlying the disease Further study of this phenomenon may reveal some "biochemical flaw" responsible for the disease

[One of us, R H F, noted that the serum lipids of patients with rheumatoid arthritis are not below normal, hence jaundice is not beneficial to arthritic patients by reason of correcting a lipid deficiency—Ed]

Effect of Pregnancy The ameliorating effect of pregnancy on rheumatoid arthritis was discussed^{100, 111} According to Dunn the relief may be correlated "most probably with the high estrogenic blood content of pregnancy" Arthritic patients may receive complete, partial or no relief during pregnancy "The estrogen content of the blood and urine in pregnancies, while always high above normal, varies widely in individual pregnancies Accordingly, a failure to obtain relief of the arthritis in all pregnancies does not invalidate its rôle"

[An attempt should be made to correlate the degrees of relief experienced by arthritic patients during pregnancy with amounts of estrogenic hormone found in their blood But it seems probable that some factor other than an increase of estrogenic substances in blood is responsible for the ameliorating effect of pregnancy—Ed]

Ocular Lesions with Rheumatoid Arthritis Of 15 cases of necroscleritis nodosa (scleromalacia perforans, scleritis necroticans) reported to date, 11 have been in patients with rheumatoid arthritis⁶ Some writers believe that the subcutaneous nodules of rheumatoid arthritis and the nodules of scleromalacia perforans are essentially similar in their early stages Eggers reported the case of a woman, aged 37 years, in whom rheumatoid arthritis and necroscleritis nodosa developed almost simultaneously Bilateral uveitis, massive hemorrhages in the vitreous, and sclerosing keratitis ensued Biopsy showed that the ocular nodules represented intrascleral abscesses "The simultaneous involvement of sclera, bones and joints need not seem strange if one remembers that all three tissues are of mesodermal origin"

No adequate reason has been given to explain why iritis and uveitis not infrequently complicate rheumatoid arthritis Hence Angevine and Rothbard^{7, 10} studied eyes and joints of rabbits infected with various bacteria In 26 of 40 rabbits arthritis developed, in 17 ocular lesions When arthritis or cyclitis occurred, synovial villi and ciliary processes were the most frequent, and usually the primary, sites of inflammation, bacteria were found therein

Amyloidosis with Rheumatoid Arthritis Amyloidosis may complicate rheumatoid arthritis or Still's disease⁷ Oxer studied two men aged 21 and 27 years who had rheumatoid arthritis of 11 and 13 years' duration, with iritis or iridocyclitis and blindness, marked anemia occurred in both cases, hepatomegaly in one At death amyloidosis of liver, spleen and kidneys was noted "Suppuration is not necessary to produce amyloidosis" Splenic amyloidosis was also found¹⁴⁵ in a case of "Felty's syndrome" [i.e. rheumatoid arthritis—Ed]

PATHOLOGIC CHARACTERISTICS OF RHEUMATOID ARTHRITIS

The pathologic physiology of joints in rheumatoid and other types of arthritis was discussed by Freund and Kelikian who described how articular structures react to abnormal stimuli

Within normal joints, resting or in motion, there is a negative intra-articular pressure equal to -60 or -70 mm of water Under pathologic conditions, such as intra-articular effusions or hemorrhage, intra-articular pressure becomes positive, as high as +70 mm of water [sometimes as high as +700 mm—Ed] The capsule becomes distended If cartilage is damaged or if bone is atrophic as in rheumatoid arthritis, the increased intra-articular pressure may push contents of the joint cavity through defects of cartilage or underlying bone If the opening is small, a flasklike excavation results, when pressure is severe and prolonged, deep cavities result In rheumatoid arthritis these cavities contain fibrinoid masses which begin to organize These ex-

cavations may be numerous and appear like epiphyseal cysts or abscesses. To prevent them effusions should be removed by aspiration or other means before too long.¹⁰⁰

[It seems to us more likely that such lesions result from enzymatic action or from the invading pannus—Ed.]

Nodules Italian rheumatologists⁴⁶⁴ believe that the subcutaneous nodules of rheumatoid arthritis resemble histologically those of rheumatic fever but that neither are specific nor diagnostic. Bennett, Zeller and Bauer contradicted this view.

"The nodules of rheumatoid arthritis and rheumatic fever differ as much from one another as do the granulomas of syphilis and tuberculosis." The nodules of both rheumatoid arthritis and rheumatic fever have certain structural and cytologic similarities, but differentiation is generally possible because one or more of the pathologic alterations usually predominate. Nodules of rheumatic fever usually exhibit injury to small blood vessels with exudation of plasma and blood cellular constituents into connective tissue, also small focal lesions similar or identical to the myocardial Aschoff nodules. In the nodules of rheumatoid arthritis marked proliferation and degeneration of connective tissue predominate, Aschoff-like nodules are rarely seen, and exudation is rarely notable. Hence the nodule of rheumatic fever, being chiefly an exudative phenomenon, tends to appear and disappear rapidly. The continued proliferation and necrosis of the nodule of rheumatoid arthritis explain its longer duration and larger size. These morphologic changes do not permit conclusions on etiology.

Muscles Pathologic reactions (an "angiomysitis") in muscles of the calf in four cases of rheumatoid arthritis were considered by Curtis and Pollard similar to those in eight cases of adult Still's disease. They are described in the section on "Still's disease."

LABORATORY DATA IN RHEUMATOID ARTHRITIS

Roentgenograms Roentgenographic features were summarized.⁵²⁹ Especially informative was the report of Forestier and Robert which cannot be adequately reviewed here. In mild cases "roentgenograms may be negative for a period of several weeks to two or three months."

Blood Counts A mild anemia of normocytic or microcytic type may appear until the disease has been active "for several weeks" (Cecil¹⁰² Rayburn). Leukocyte counts may be from 12,000 to 20,000 in a presumably acute pain condition, 4,000 to 11,000 in chronic cases. The percentage of nonfilamentous cells was more than 16 per cent (maximal normal) in 63 per cent of cases, and more than 8 per cent in 88 per cent of 392 cases. "A normal filament count usually excludes active rheumatoid arthritis."¹⁸³

Among normals, according to Stiles, Dirickx and Stiles, the nonfilamentous neutrophils range from 2 to 5 per cent of the total number of leukocytes, with a mean value of 4.1 per cent. Filamented neutrophils range from 55 to 66 per cent, with a mean value of 60.6 per cent. The nonfilament-filament ratio (nonfilamentous neutrophils times 100 divided by filamented neutrophils) ranges from 3 to 9 (normal mean 7). In 14 cases of rheumatoid arthritis the mean nonfilament-filament ratio was 36.9, a significant increase.⁵⁴⁰ This ratio was found to be a more sensitive indicator of arthritic variations than the sedimentation rate, but the latter is of more fundamental significance. When remissions occur, the nonfilament-filament ratio

may fall but the sedimentation rate may remain elevated for some time, a warning that conditions are not yet normal

Sedimentation Rates It is generally agreed that sedimentation rates of erythrocytes are increased in practically all cases of rheumatoid arthritis^{183, 464}

Of 568 cases noted in the literature rates were increased in 92 per cent (Rates were normal in 60 per cent of 254 cases of osteo-arthritis, in 75 per cent of 149 cases of fibrositis) Rates may not be increased during the first weeks in acute cases or during the early months in the more insidious cases¹⁸³ The mean rate in Stile's 14 cases was 37.3 mm (Westergren method, uncorrected for anemia) But rates were normal in 50 per cent of 435 ambulatory patients with rheumatoid arthritis seen by Weil, Smith, King and Wooton who considered the value of the test overrated [The reported details of these cases were meager—Ed] Rates varied from 20 to 125 mm (Westergren method) in 43 active cases, from 8 to 20 mm in eight arrested cases reported by Davison, Woolley and Donovan who noted no constant relationship between sedimentation rates and concentrations of plasma proteins Repeated blood transfusions were followed by reduction in sedimentation rates without improvement in plasma protein relationships

Serum Proteins Most of the patients of Davison, Woolley and Donovan exhibited increased fibrinogen and serum globulin, normal serum albumin (reputedly generally increased),¹⁸³ normal total proteins and reduced albumin-globulin ratios There were many exceptions, however, as shown in table 2 [and as noted in our last Review—Ed]

TABLE II
Values for Serum Proteins*
(Davison, Woolley and Donovan)

	Normal Controls (7)	Rheumatoid Arthritis	
		Clinically Inactive (8 cases)	Active (43 cases)
Serum fibrinogen	0.2-0.4	0.3-0.6	0.2-0.8
Serum albumin	4.6-5.6	4.7-6.0	2.4-7.1
Serum globulin	1.9-3.0	0.4-2.9	0.3-5.1
Albumin-globulin ratio	1.7-2.5	1.5-14.3	0.6-15.0
Total proteins	6.6-8.3	5.7-10.0	5.0-9.8

* All values except albumin-globulin ratio expressed in grams per 100 c c of serum

Miscellaneous The formol-gel test provides a simple qualitative test for increased globulin or fibrinogen in the blood It depends on the change in viscosity of blood fluids after the addition of formaldehyde⁶ Normal serums and plasmas undergo little if any physical change, but specimens containing excess globulin or fibrinogen undergo a marked increase in viscosity which may induce complete coagulation or irreversible gelation of the fluid Scull and Pemberton noted that gelation generally occurred in cases of rheumatoid arthritis and to a more marked degree than in cases of osteo-arthritis There was a significant association between formol-gel reactions and sedimentation rates when the former were negative, the latter were generally normal

[We believe that sedimentation rates provide the more accurate index of clinical activity of the disease—Ed]

Serum phosphatase is generally normal in chronic arthritis⁷ Some workers have noted normal values in rheumatoid arthritis, increased values in osteo-arthritis⁵⁸⁸

Watson considered normal values to be up to 50 Bodansky units per 100 c c of serum. Among 45 patients with "chronic arthritis" (types not separated) values ranged from 4.4 to 14 (average 9.1) units.

ETIOLOGY AND PATHOGENESIS OF RHEUMATOID ARTHRITIS

Factor of Infection 1 *Foci* Of 53 cases of rheumatoid arthritis in which foci had been removed previously Bach found the following infected foci still present: gingivitis in 44, infected teeth in 25, infected dental roots in 10, infected tonsils in 11, infected tonsil tags in nine, sinusitis in 11, cholecystitis in five, cholelithiasis in four, prostatitis in seven of 17 males, cervicitis in seven of 36 females. Of these 53 patients only two had no infected foci, 10 had one, 14 had two, 19 had three, six had four. [This adds up to only 51 patients—Ed.] Examination for, and removal of, foci too often are hastily and incompletely done.

By using certain in vitro tests Stiles and Chapman recovered bacteria, considered pathogenic, from various foci in 16 cases of rheumatoid arthritis: *Staphylococcus aureus* from nose in 44 per cent, from oral cavity in 19 per cent, alpha streptococci from feces in 38 per cent, from nose in none. Similar organisms were as readily found in foci of patients with a variety of chronic illnesses.

Four writers^{22, 144, 508} considered infected gall-bladders a significant focus in arthritis. Peers obtained abnormal cholecystograms in 13 of 25 cases of rheumatoid arthritis (in 13 of 21 cases of osteo-arthritis). Willard and Strawbridge considered studies of biliary drainage a necessary adjunct to cholecystograms. Pathogenic organisms (*Escherichia coli* or *Bacillus coli*, *Staphylococcus aureus*, nonhemolytic or green-producing streptococci, a member of the salmonella group) were found in biliary drainages from 35 per cent of 29 patients with "arthritis" (type not stated).

[No data were given to show whether these patients were relieved of their arthritis when gall-bladders were removed. Very few patients with cholecystitis develop rheumatoid arthritis. Other writers¹ have previously noted no permanent benefit from removing infected gall-bladders in cases of rheumatoid arthritis—Ed.]

It must take more than an infected focus, however, to produce arthritis. In 63 per cent of 239 psychiatric patients ("physically well," that is, "mentally rather than physically ill") C. H. Brown found infected foci. Yet none of these patients had arthritis. Infected foci were found in the nose and throat in 44 per cent of these cases, in the teeth in 37 per cent, in female pelvic organs in 22 per cent, in urinary tract in 17 per cent, in cardiorespiratory system in 2 per cent, foci of infection in chests were rare.

2 *Cultures of Blood and Joints* Findlay and his colleagues could not isolate pleuropneumonia-like organisms from the synovial fluid of four patients with rheumatoid arthritis or from the pleural and pericardial exudates from two other rheumatoid patients.

3 *Precipitins* In 69 per cent of 32 cases Bruce and Caswell found precipitins to hemolytic streptococci in high titer in serum, similar precipitins

were found in only four of 15 cases of osteo-arthritis, in none of 10 normal controls. The presence of these precipitins was considered indirect evidence that streptococci play some, possibly an etiologic, rôle in the disease, or such precipitin reactions may be specific for rheumatoid arthritis but without etiologic significance.

4 Agglutinins In 72 cases Bunim and McEwen studied the agglutination titer for hemolytic streptococci: in 14 it was negative, in four, 1:20 or 1:40, in the others (75 per cent) significantly elevated: 1:80 or 1:160 in 23, 1:320 or 1:640 in 31 cases.

5 Antistreptolysins In most of the 72 cases of Bunim and McEwen antistreptolysin titers were not abnormal. In normals the median titer was 25 units, the normal maximum was 100 units. Antistreptolysin titers were 100 units or less in 61 cases, 150 to 400 units in 11 cases of rheumatoid arthritis. These generally normal values contrasted sharply with the elevated agglutinin titers. In three-fourths of the cases of high agglutinin titers antistreptolysin titers were normal. Since no correlation was noted between the antistreptolysin titer and the stage of the disease or severity of illness, such titers were of doubtful prognostic import.

6 Antifibrinolysins Antifibrinolysin titers were normal in 161 of 171 tests made by Perry⁴⁵¹ in 33 cases of rheumatoid arthritis, in only two cases were abnormal titers found and these were only transient. These results are in striking contrast to those in rheumatic fever.

[In other words these data do not support the idea that hemolytic streptococci cause rheumatoid arthritis, and are evidence against the idea of a common etiology of rheumatic fever and rheumatoid arthritis—Ed.]

Theory of Bacterial Allergy Italian work reviewed by Ravenna yielded no support to this theory. But Cecil believes that the theory needs further study and in its support cited unpublished work of Angevine and Rothbard on the sensitization of joints of animals to experimental arthritis.

Virus Theory No data appeared.

Factor of Trauma This was not discussed.

Factor of Circulatory Disturbance The abnormal sugar tolerance curves commonly found in cases of rheumatoid arthritis have been considered caused by circulatory disturbances in finer vessels rather than by disturbed pancreatic function^{461, 468}. To verify this concept Dandurand, Scull and Pemberton applied to the blood of 55 rheumatic patients (23 with rheumatoid arthritis, 14 with osteo-arthritis, 11 with "mixed arthritis," three with fibrositis, four with miscellaneous rheumatic conditions) the test of Polonovski and Warembourg (1933) for fractionating the glucose and non-glucose materials in blood which reduce chromic acid. The blood plasma of these "rheumatisants" regardless of type, generally possessed an excess of reducing substances other than glucose. Wide individual variations were found, the significance of which was not clear. Tests were repeated after the ingestion of glucose. Results were interpreted as indicating that delayed

responses to the sugar tolerance test reflect circulatory alterations, not a primary disturbance in carbohydrate metabolism

Factor of Altered Metabolism Advocates of sulfur therapy have reported that a deficiency of sulfur exists in nails, articular cartilage and other tissues of arthritic patients, indicating an abnormal sulfur metabolism. But these reports have given meager or contradictory data. The careful, detailed studies of Freyberg, Block and Fromer in four cases of rheumatoid arthritis, two of osteo-arthritis, three of ankylosing spondylitis and on four normal controls led to opposite conclusions as follows

No evidence of sulfur deficiency or abnormality of sulfur metabolism exists in arthritic patients. There is no obvious biochemical or metabolic indication of a need for, or benefit from, sulfur in the treatment of arthritis. The distribution of urinary sulfur was about the same among these various patients and controls except that arthritic patients eliminated a slightly higher percentage of sulfur in conjugated form. Even if the difference were significant, it does not indicate a deficiency of sulfur for purposes of detoxication or any impairment of the detoxifying function in cases of arthritis. The effect of colloidal sulfur injected intravenously was about the same on arthritics and controls. Since the excretion of sulfur increased by amounts greater than those injected, the intravenous injection of colloidal sulfur assuredly would not benefit or prevent sulfur deficiency if it existed. Since no consistent significant increase in excretion of conjugated sulfur resulted, significant detoxification cannot result from such injections. When colloidal sulfur was injected intramuscularly, more than the amounts injected appeared in urine, hence such injections tended to increase rather than prevent sulfur deficiency. No notable change in excretion of conjugated sulfur occurred. Whether given by vein, muscle or mouth, colloidal sulfur was metabolized and excreted in the same way, indicating no advantage to its parenteral use. The cystine content of finger nails was normal in most cases of arthritis, unexplainably low in a few. But the administration of large amounts of colloidal sulfur or sulfur containing salts did not increase the cystine content of nails.

[This excellent study indicates the complete irrationality of sulfur therapy for arthritis. If those who would propose a "new form" of treatment would only carry out careful studies such as this before advocating the new remedy, physicians and patients would not have to waste so much time and money on useless remedies and therapeutic fads—Ed.]

Factor of Vitamin Deficiency 1 Vitamin A Patients with rheumatoid arthritis were found by Race⁵ to be deficient in plasma vitamin A. Using a different method, Hall, Bayles and Soutter noted a borderline to severe vitamin A deficiency in 65 per cent of 79 cases. In 45 cases the degree of vitamin A deficiency roughly paralleled the severity of the disease as indicated by sedimentation rates.

Race⁵ studied his cases by means of the light-extinction density. Direct chemical and spectrographic methods for measuring the quantity of vitamin A are inaccurate. Vitamin A unites with proteins in retina to form visual purple. This continuous process depends on a sufficiency of the vitamin. The rate of formation of visual purple after exposure of the retina to bright light depends on the vitamin A available. The increasing ability to see in dim illumination after exposure to bright light is "dark adaptation", the measurement of this function is the basis for methods used for indirect evidence of vitamin A deficiency. By this method normal controls give initial biophotometer readings of 0.50 millifoot candles or less. The average reading of 13 controls was 0.32. That of 79 patients with rheumatoid arthritis was 0.78, readings in

the 79 cases of rheumatoid arthritis were normal in 35 per cent, between 0.50 and 1.00 (borderline or subnormal) in 35 per cent, between 1.00 and 1.50 (moderate deficiency) in 21 per cent, more than 1.50 (severe deficiency) in 9 per cent. Those patients who were notably deficient in vitamin A did not have xerophthalmia or keratomalacia, one had night blindness. Normal adults require 2,000 to 4,000 units of vitamin A daily, average well rounded diets contain 6,000 units but many of these arthritics required 4 to 11 times that amount (25,500 to 68,000 supplemental units of vitamin A as halibut liver oil) to maintain normal dark-adaptation curves. It is not clear whether this increased need for vitamin A represents increased utilization, decreased absorption or an inactivation of the vitamin (Hall, Bayles and Soutter)

2 Vitamin C The plasma content of ascorbic acid of only one of Jacques' 48 patients with rheumatoid arthritis was normal (0.7 to 0.9 mg per 100 c.c. of blood), in the remaining 47 it was subnormal (0.37 to 0.68 mg, average 0.42 mg per 100 c.c.) (In 18 of 20 cases of osteo-arthritis levels were more than 0.7 mg, average 0.92 mg). Secher also reported that his "patients with rheumatic arthritis generally had no ascorbic acid in the blood," an abnormality noted in other diseases as well. Secher noted abnormal sugar tolerance curves ("decreased tolerance for sugar") in cases of arthritis and also other diseases "which had only one feature in common with arthritis no ascorbic acid in their blood." But when sufficient ascorbic acid was given to restore the normal ascorbic acid level in blood, sugar tolerance curves became normal. "It may therefore be assumed that the cause of the abnormal blood-sugar curves described by Pemberton [in arthritics] is a deficiency of ascorbic acid, and it is on this deficiency that the shape of the curves depends."

[Secher gave few figures to support this important conclusion. We will await with interest further studies on the correlation between deficiency of ascorbic acid in blood and abnormal sugar tolerance curves—Ed.]

Intestinal Toxæmia Wiltzie upheld the idea that streptococci from primary foci invade the body to form secondary foci in colon, liver and elsewhere.

[This report combined many quotations of others and much hypothesis but little or no evidence to support its hypothesis—Ed.]

Factor of Endocrine Abnormality For reasons which cannot be adequately reviewed herein Helfet stated his belief that the pathogenesis of rheumatoid arthritis may involve abnormal parathyroid function, or "secondary hyperparathyroidism." He noted certain features (advanced osteoporosis, "bone changes not dissimilar to fibrocystic disease," passage of a calcium phosphate stone) present in two cases of rheumatoid arthritis and cited the reports of Oppel (1926), Ellis (1927), Schkurov (1935) and Leriche (1935), some of whose reports we have previously criticized^{3,4}. Helfet admitted that there is little biochemical evidence that the parathyroid gland plays a critical rôle in rheumatoid arthritis.

Psychogenic Factor McGregor gave case-examples in which the onset or flare-up of rheumatoid arthritis bore a close time relationship to some emotional episode.

Many arthritics are emotionally unstable before the onset of their disease. Considering the profound changes in one's outlook on life which arthritis may produce, modifications of personality may be expected. But often some emotional crisis seems actually to precipitate the disease. Among several reasons for ascribing etiologic importance to psychologic factors are two: (1) the potency of the mind in producing and maintaining (for various reasons, e.g. sympathy, sickness benefits) such symptoms as pain and stiffness, (2) the fact that emotional conflict can disturb the endocrine and the vegetative nervous systems. But "there is nothing conclusive in establishing a relation between emotional events and attacks of rheumatism unless it can be shown that such a relation is peculiar to the disease in question. At present this has not been done." Meanwhile, regardless of whether emotional disturbances among arthritic patients are of primary or secondary etiologic importance, many will not respond adequately to treatment until their psychologic problems have been attacked properly.

Conclusions on Etiology In Italy "the prevalent opinion is that rheumatoid arthritis is a true infectious disease; the fact that the causative agent has not yet been found does not mean that it does not exist."⁴⁶¹ According to Pemberton and Scull the streptococcal antibodies present in the serums of patients with rheumatoid arthritis are "not to be dismissed from consideration, but their etiologic importance must be interpreted conservatively as non-specific until more direct evidence is at hand." Impressed by the ameliorating effect of jaundice and pregnancy on rheumatoid arthritis Osgood concluded that "the chances are better that the unknown etiologic or X factor which we know exists but which we have thus far been unable to discover will prove to be a biochemical rather than a bacterial factor."

[Obviously the cause of the disease remains unknown—Ed.]

RELATIONSHIP BETWEEN RHEUMATOID ARTHRITIS AND OTHER DISEASES

Rheumatic Fever Some physicians have used the similarities between the histologic structure of the nodules of rheumatic fever and rheumatoid arthritis as evidence that rheumatic fever and rheumatoid arthritis are closely related conditions. This view was not supported by the study of Bennett, Zeller and Bauer.

Still's Disease This will be discussed in the section on "Still's disease."

TREATMENT OF RHEUMATOID ARTHRITIS

General Remarks The attitude toward treatment which physicians and patients must have was defined by Chaney, Hench, Horder, Pemberton, and Westcott:

Physicians must discard the idea that "nothing can be done for chronic arthritis." Too many physicians approach their arthritic patients with this wrong frame of mind; they are whipped before they start and the patient often senses it. The overwhelming experience of those who really try to do something for these patients refutes such a pessimistic notion. But physicians must realize that there is no rapid sure cure for the disease and that no one remedy or combination of remedies

is always effective. Treatment based on one hypothesis alone (e.g., the infectious or the metabolic hypothesis) will almost surely fail. He who concentrates on a single remedy (vaccine or diet) is likely to become a faddist. Physicians should treat each patient as an individual problem, rely on procedures of known value and avoid the hasty use of new "cures." These "cures" are much more valuable to their manufacturers than to the patients who use them. Most highly recommended "new remedies" have been shown in time to be of limited or no value. The disease is not cured by a "bottle of medicine" for internal use and a liniment for external use. The physician should select remedies to fit the patient as well as the disease and should subject the patient only to those measures which the stage of his disease and his psychology, constitution and finances warrant.

Patients must also have a definite understanding of just what can and what cannot be done. Some patients have a maximum of expectation and a minimum of tolerance toward their physician. Others have a minimum of expectation and a maximum of suspicion. The patient must possess confidence in his physician and a certain optimism toward therapy. He must not expect a rapid cure. He cannot placidly munch pills or passively accept a vaccine to the exclusion of other measures. He must make positive efforts on his own behalf. He should accept an initial selection of conservative measures of known value. He must not expect that under treatment his condition will improve constantly and without interruption; he must expect some variability in his response to therapy. He does have a right to expect therapeutic versatility on the part of his physician, and he should expect changes in treatment if and when necessary. But he must not expect some new, diverting treatment every little while. To give any plan of treatment a fair chance he should accept it for at least four months, and the final evaluation of any treatment should not be made for at least two years.

Management of Foci Credit for being the first to cure rheumatic or other pains by removing infected foci has been given variously to Hippocrates,⁸³ Ashur-bani-apal, a seventh century Assyrian king,⁴⁸⁵ and Benjamin Rush.⁷⁰

[Many recent writers have cited Hippocrates as having relieved two patients with rheumatism by extracting teeth, but not one of these writers has given the original reference. One of us, P. S. H., has tried repeatedly but vainly to find this reference in available translations of Hippocrates and by correspondence with those who have passed this citation along. Can any reader supply the reference or is Hippocrates, once more, being credited with something he did not do?—Ed.]

Arguments against the practice of removing infected foci are becoming more vigorous.^{232, 435, 469} Two reports in particular were critical of the theory of focal infection as a cause of rheumatoid arthritis. Haden wrote: "It seems more and more evident to critical observers that focal infection is concerned only as an influencing factor in rheumatoid arthritis and is not the point at which a specific organism causing the arthritis is harbored. If the infection does get in through the throat, it seems to do so after removal of tonsils as well as before. It is possible that focal infection is more important early in the course of the disease than it is later." Haden considered preceding or coincident infections, especially with hemolytic streptococci, the most frequent precipitating factor. "It seems possible that a toxic protein may be the immediate source of the joint inflammation such as is known to occur in the arthritis of serum sickness."

Even more critical was the report of Reimann and Havens on "the case against indiscriminate removal of teeth and tonsils" in rheumatoid arthritis and other diseases supposedly caused by infected foci. Although tonsils are often removed as a matter of routine, there is no evidence of the specific value of the procedure in rheumatoid arthritis. No studies have been made with adequate controls, and too little is said of the actual harm which tonsillectomy may do. Summarized was cumulating evidence "throwing grave doubt on the practice of removing tonsils or teeth in the hope of preventing the onset or influencing the course of rheumatoid arthritis." With others Reimann and Havens have become skeptical of the bearing of focal infection in this disease. They concluded that harmful effects from tonsillectomy occur more often than is generally known. 85 deaths occur annually as a result of tonsillectomy on children less than 15 years of age, in one group of cases cited, 57 per cent of deaths from anesthesia occurred during tonsillectomy on children, from 40 to 60 per cent of pulmonary abscesses follow tonsillectomy and other oral operations, tonsillectomy and alveolectomy may lead to temporary bacteremia and bacterial endocarditis. The writers concluded that the experience of 25 years had not proved the value of removing infected foci in rheumatoid arthritis. The procedure should be recommended only in "exceptional cases when evidence of actual local disease is present and its relation to remote or systemic disease probable." Even then the removal of local infections in the hope of influencing remote or general symptoms must be regarded as an experimental procedure not devoid of hazard. Many foci of infection heal after the patient recovers from systemic disease, or when the general health is improved with hygienic and dietary measures.

[This critique would have been more forceful if it had included original data, case reports, statistics, and so forth on the author's own failures and disasters following removal of infected foci. The paper comprises chiefly a compilation of the opinions of others unfavorable to the theory of focal infection. As such it is a valuable résumé, but it is regrettable that the writers made no attempt to marshal convincing evidence of their own —Ed.]

Some of those who are now belittling the theory of focal infection (e.g., Cecil, Haden) were formerly among its staunchest advocates. [Their frankness in explaining the reasons for their about-face is commendable and lends considerable weight to their current views. But if they were wrong once they may not yet be entirely right —Ed.] Many physicians may react to these "conversions" as did Pemberton who, to say the least, has never been accused of being an enthusiast concerning the removal of infected foci, and who has for years sought to restrain the medical profession's enthusiasm for the theory of focal infection. Pemberton now writes "It is a rather curious commentary upon the present situation that the writer now finds himself in the position of endeavoring to stem the growth of such an iconoclastic attitude as would sweep away all consideration of the rôle that focal infection plays in arthritis. The pendulum of medical opinion seems always to be swinging from one extreme to another. We are [now] in danger of doing injustice to hosts of arthritics through shortsighted neglect of the limited but definite rôle of focal infection in this and in other diseases."

[All of which probably leaves most of us about where we have been —Ed.]

Haden agreed that definitely infected foci should be removed "on general principles." This should be done in mild cases as early as possible but in the more severe cases only at the optimal time, that is after the patient is

properly "built up," after "physiologic equilibrium" has been more nearly restored by a preliminary program of rest in bed, dietotherapy and other measures^{22, 272, 447} There are "rare severe cases in which the ravages of focal infection are so marked that no option remains but to proceed at once with whatever measures may be necessary"⁴⁴⁷ It is the duty of the internist, not the "focal specialist" alone, to evaluate foci and determine how and when they shall be treated Pemberton has seen "many instances" in which premature removal of foci precipitated a serious flare-up

[Not a few writers have made such statements It is unfortunate that statistics thereon are rarely if ever given—Ed]

1 Teeth Treatment of gingivitis is as important (if not more so) as the removal of infected teeth^{22, 34, 447} Infected teeth and pulpless teeth with apical infections should be removed^{22, 34} Some^{272, 409} considered the removal of "questionable teeth" unwise "decreased density about a dental root is no more proof of infection there than is increased density in the case of nasal sinuses The cultivation of bacteria from teeth gives little information since the bacteria usually present have no proved relation to the arthritis" Bach considered the removal of such teeth justified in progressive arthritis "It is the exception rather than the rule to note dramatic improvement after removal of dental foci, nevertheless they should be removed to 'lessen the patient's load' and not to cure the arthritis per se"¹²⁹

2 Tonsils Methods to determine tonsillar infection^{22, 443, 469} and the occasional harmful effects of tonsillectomy⁴⁶⁹ were noted Infected tonsils of young patients should be removed, but the tonsillar infection of older patients and those who refuse tonsillectomy can be successfully treated by irrigations, expressing secretions and applying germicides according to Bach and Beir Adenoids may be as infected as tonsils²² According to Bach infected lingual and pharyngeal lymphoid tissue is the cause of throats which are "scratchy" even after tonsillectomy Beir considered neglect of infected lingual tonsils and adjacent lymphoid tissue the greatest cause for failure to relieve patients by focal removal Of his 18 patients with rheumatoid arthritis whose tonsils were removed 44 per cent were "cured," "all others were greatly improved"

3 Sinuses Methods for determining sinusitis were described Roentgen therapy is sometimes successful²²

4 Gall-bladder If infection of gall-bladder is definite in cases of arthritis, gall-bladders should be removed, otherwise medical treatment is indicated (low fat diet, cholagogues, e.g., decholin, repeated drainage, autogenous vaccines) Under such treatment gall-bladders may become normal, according to Willard and Strawbridge

[They give no statistics as to the improvement of arthritis thereby, one case only was cited in which joints and gall-bladder cleared up under such therapy—Ed]

5 Intestines Two writers^{22, 605} believed that intestines may act as foci But cultures of stool rarely give useful information²²

6 Prostate The determination of genito-urinary infection was discussed^{22, 606} Prostatitis, "common secondary focus," should be treated especially in cases in which joints are temporarily aggravated by prostatic massage incident to examination²²

7 Female Pelvis The conservative and radical therapy of pelvic infection was discussed²² Pelvic heating by local diathermy was recommended¹⁴⁶

Results of Focal Removal As usual practically none of the advocates of focal removal gave statistics on results Pavey-Smith wrote "If an infected tonsil is removed within six months of the onset of the rheumatism a com-

plete cure is probable" Beir claimed to have cured 44 per cent of his patients by treating the lingual tonsils. It is difficult indeed to share this enthusiasm. Generalizations do not settle the argument.

Vaccines, Antigens, Filtrates The year's literature revealed few protagonists of vaccine therapy. Autogenous vaccines of alpha hemolytic streptococci were used by Hindley-Smith²⁰⁸ there were "few cases" in which results were not successful [No statistics given—Ed]. But autogenous vaccines according to Small are in each case an untried product which adds one more variable to the procedure. He favored the use of stock vaccines [presumably of his indifferent streptococci (Small, 1929)—Ed] given in microdoses of only 10 to a few hundred organisms, not thousands or millions thereof. When a patient is doing well dosage must not be increased [no statistics on results given—Ed]. One hundred patients with "chronic arthritis" [types not stated—Ed] were given by Schallig staphylococcus-streptococcus undenatured bacterial antigen. 65 per cent were "completely relieved" by 10 weeks' treatment, 28 per cent obtained a "favorable result" within 25 weeks, "only seven patients failed to benefit."

To others results of vaccine therapy have been "uniformly disappointing"⁴⁵⁴ or "disturbingly confusing", the reports were less "rosy" in direct ratio to the carefulness of the investigator⁴⁵⁵. Their value has been unduly emphasized by those who regard the arthritic patient as "a victim of a spray of streptococci"¹⁴⁷. Certainly vaccines are not "specific"^{282, 258}
^{282, 104, 507}

Strong evidence suggests that the value of vaccines in arthritis is chiefly from the psychologic effect of the injections. Sidel and Abrams gave a polyvalent streptococcal vaccine to 25 patients with rheumatoid arthritis, 68 per cent improved. But injections of saline solution improved 72 per cent of 33 patients with rheumatoid, and 86 per cent of 64 patients with osteoarthritis. Margolis and Eisenstein questioned 83 members of the American Rheumatism Association of these only 59 stated that they used vaccines for rheumatoid arthritis. Many now use vaccines much less often than previously. About 60 per cent of those who used vaccines considered them beneficial, but less than 50 per cent of patients are helped thereby. Margolis and Eisenstein no longer use vaccines "vaccines give the patient a false sense of security on which he may rely too much". One writer²⁵⁸ published his code for the use of vaccines in rheumatoid arthritis: the physician should never claim that the vaccines are specific or will "cure" the patient; the cost of such therapy should never be burdensome, vaccines should never be relied on alone or used as a form of "occupational therapy" just for something to do. He who breaks this code is in danger of being considered a "vaccine racketeer."

Foreign Proteins Protein shock by means of triple typhoid vaccine aims at stirring up the patient's immunity mechanism "and hoping for the best."¹⁷⁷ Such therapy was considered useful in selected cases^{232, 258}. Straus preferred intradermal injections of lactalbumin.

Bee Venom Of 50 patients with "chronic arthritis" (30 infectious, 15 menopausal, 5 traumatic) given bee venom by Goldbeig, 60 per cent were "definitely benefited," more so than were 22 patients given 40 to 60 grains of salicylates daily. Others reported good results in one case each^{378, 415}. Hill considered bee venom of no definite value, it is "a counterirritant and probably nothing else."³⁸⁰

Cobra Venom Macht (1938) recommended the use of cobra venom to relieve pain in certain conditions including arthritis. Steinbrocker and colleagues gave such injections to 13 patients with rheumatoid arthritis. 11 received "slight to moderate" relief, two were unrelieved. Of nine control patients with rheumatoid arthritis given saline injections, none were improved.

[This contrasts with the report of Sidel and Abrams who improved 72 per cent of 33 rheumatoid patients with saline injections. It shows how difficult it is for even the fairest investigator to exclude the personal equation when evaluating any remedy for this disease. It is probably not unfair to say that Sidel and Abrams were of a mind to show that injections of saline solution were as good as vaccines (i.e. that vaccines were no better than saline), whereas Steinbrocker and his associates were convinced that injections of saline solution were valueless compared to cobra venom. These attitudes may have unconsciously influenced the interpretation of the results.—Ed.]

Diet There is no specific diet. Scull condemned "the bizarre dietary measures based on doubtful premises and exploited in uncritical quarters." The low carbohydrate, high vitamin diet was discussed^{50, 188, 282, 483}. The incidence of food allergy among rheumatic patients is not significant⁴⁹⁵.

Vitamins Patients with rheumatoid arthritis, like those with certain other diseases, often possess subnormal amounts of vitamins in their plasma. These deficiencies are not specific nor of etiologic importance. The supplemental use of vitamins readily corrects the plasma deficiencies but has not significantly affected the joints. There is no "antirheumatism vitamin." "We shall need soon a little debunking of vitamin cure-alls" (Osgood). Of course patients should secure their daily basal requirements: at least 6,000 international units of vitamin A, 250 international units of vitamin B₁ (0.75 mg of thiamine hydrochloride), 300 international units (100 mg) of ascorbic acid⁴⁹⁵.

1 **Vitamin A** The susceptibility of rheumatic patients to upper respiratory infections may represent a deficiency of vitamin A⁴⁹⁵. The deficiencies noted by Hall, Bayles and Soutter were readily corrected with doses of 25,500 to 68,000 U. S. P. units daily but these doses did not alter the arthritis.

2 **Vitamin B** Supplemental doses were recommended unenthusiastically^{419, 503}.

3 **Vitamin C** To 47 rheumatoid patients with low concentrations of ascorbic acid in plasma Jacques gave 100 mg by parenteral injection daily for one week and 300 mg by mouth daily for one month. Plasma deficiencies were corrected but no marked effect on joints was noted. Muether's experience was similar. Secher claimed that by giving ascorbic acid he could restore blood sugar tolerance curves to normal and minimize toxic reactions to chemotheapy, but he made no claims that joints were improved by the vitamin per se.

4 Vitamin D Muether's results with vitamin D (type not stated) were "most unconvincing", he considered the use of large doses dangerous and irrational as did Abrams and Bauer⁶ But Snyder and Squires claimed that there are notable differences in toxicity and therapeutic potency in vitamin D (ertron) as made by the Whittier process and other vitamin D products (viosterol, diisdol, calciferol) prepared by ultraviolet radiation of ergosterol (as used by Abrams and Bauer)

[Further evidence is needed to support this claim—Ed]

Snyder and Squires gave from 100,000 to 600,000 (average 300,000) U S P units of ertron daily for four to 18 months to 12 patients with rheumatoid arthritis (and to 11 with osteo-arthritis) unrelieved by other measures Results were excellent in four cases, good in four, slight in four with rheumatoid arthritis (excellent in one, good in five, slight in three and absent in two with osteo-arthritis) No serious toxicity occurred It was suggested that the products used by Abrams and Bauer⁶ and others might have derived their toxicity from small traces of toxisterol therein Estimations of blood calcium, phosphorus and sedimentation rates were made before and after treatment, but changes therein could not be correlated with the degrees of improvement noted

[Snyder and Squires admittedly studied no control series of patients treated with other forms of vitamin D But other writers have also only used one favorite form Of the cases of Snyder and Squires sedimentation rates dropped notably in only two, slightly in four, and rose in six, sometimes notably This suggests that a fundamental error in the disease was not corrected despite some clinical improvement—Ed]

Additional intestinal treatment—Colonic irrigations were advocated by only three physicians^{22, 387, 605} Wiltsie insisted that the failures of others were due chiefly to improper technic for such irrigations His "improved method" was described He considered implantation of acidophilus cultures useless as "this does not influence streptococci, the organism usually responsible for the disease" [not proved—Ed]

Endocrines Cortin, 3 to 5 c c, was given by Watson intramuscularly weekly to 12 patients with "chronic nonspecific arthritis" Elevated serum phosphatase values were reduced to normal and "more or less pronounced clinical improvement" occurred When treatment was discontinued [after an unstated time—Ed] phosphatase levels rose and articular symptoms increased Desoxycorticosterone acetate did not produce similar results

[Details were meager—Ed]

Estrogen was given by Cohen, Dubbs and Myers to 17 patients with rheumatoid arthritis alone, and to six with rheumatoid arthritis and osteo-arthritis Daily, later weekly, intramuscular injections of 10,000 to 100,000 international units were given Total dosage varied from 50,000 to 850,000 international units Of these 23 patients 12 noted "distinct improvement in joint symptoms," three improved some and then relapsed, seven were not relieved and one became worse Those who had menopausal symptoms noted relief thereof Twelve additional patients with rheumatoid arthritis but without any menstrual disturbances received 50,000 international units daily for 7 to 21 days without relief Unless patients with rheumatoid arthritis also have disturbed menstrual function, little benefit is to be expected from estrogen therapy Such poor results may be due to inadequate dosage, according to Dunn who recommended giving 20,000 to 30,000 rat units (100,000 to 150,000 international units) every third day for nine days

to arthritic patients with symptoms of menopause Dunn also recommended the use of thyroid in "arthritis" with hypothyroidism

[No detailed results were reported The writer was not specific as to what types of "arthritis" were treated and as to whether the symptoms relieved were articular or menopausal It would appear that only menopausal symptoms were relieved—Ed]

Miscellaneous Medicines Haden still considered neoarsphenamine (0.3 to 0.4 gm twice weekly for three to five weeks) the most valuable drug of all "In order to reduce the intake of phosphorus and thus remove the stimulus to the overproduction of parathormone" which he considered a possible cause of rheumatoid arthritis Helfet gave aluminum acetate (average dose, 1 drachm of a 2.5 per cent solution 4 times a day for several weeks) to 15 rheumatoid patients No ill effects were noted, overdoses can produce rickets Results were "encouraging" Of the 15 patients 9 were "greatly relieved" No significant roentgenographic or biochemical changes were noted

[Relief was noted by 9 of 15 patients, i.e., 60 per cent Is this "the inevitable 60 per cent" who improve under almost any treatment? Further studies will be awaited with interest The author admitted that "the theoretical basis for treatment by this means was not definitely established" In the gastrointestinal tract aluminum would precipitate phosphorus and thus interfere with its absorption The continued administration of aluminum might produce a deficiency of calcium and phosphorus—Ed]

Hematonic Transfusions To combat hypochromic anemia ferrous sulfate (3 grains three or four times daily) was given This will fail if anemia is from faulty utilization of iron (rather than from faulty absorption), if so, transfusions (two or more, a week apart) may be helpful^{183, 282}

Those Other "Remedies" *Pharmaceutical Step-Children* Causalin, which contains aminopyrine and which has been condemned previously^{5, 6, 7} caused another death, that of an arthritic woman who took about 90 capsules in one month, agranulocytosis (leukocytes down to 600 per cubic millimeter) developed⁴⁷ Aciform II, also previously condemned,⁷ was given by Scully to seven patients with rheumatoid arthritis Results were "complete recovery" in one, "marked improvement" in three, little or no improvement in three These patients also received hydrotherapy and aspirin [which probably caused the relief, not the aciform—Ed]

Sulfur Preparations Studies by Freyberg, Block and Fromer demonstrated conclusively that there is no rationale to this treatment, in rheumatoid arthritis no primary disturbance of sulfur metabolism exists Colloidal sulfur in small or large doses does not significantly affect the disease

Colloidal sulfur (sulisocol) was given, generally intravenously, by Abrams and Bauer to 14 patients Total doses were generally 310 to 370 mg within two months, three patients received large doses totalling 1,080 to 2,980 mg No toxic reactions occurred Transient subjective improvement was noted by some patients, but none improved objectively and sedimentation rates of the majority were not altered significantly Of the members of the American Rheumatism Association questioned by Margolis and Eisenstein more had abandoned sulfur than were using it Results noted during sulfur therapy are either psychogenic or from spontaneous remissions

Chrysotherapy (Gold Salts) The use of gold salts is now one of the most interesting and contradictory features of the study of rheumatoid arthritis. Detailed analysis of results in 105 American cases^{185, 200, 585} and 60 British¹⁷⁶ appeared, also comments, without statistics, on the treatment in more than 200 other American cases^{102, 382, 434}

1 Indications Rheumatoid arthritis, Still's disease and psoriatic arthritis are considered amenable to chrysotherapy, in ankylosing spondylitis and osteo-arthritis results are debatable^{185, 508}, chrysotherapy is not useful in fibrositis or the specific arthritides

2 Contraindications These remain as stated in previous Reviews but they were listed again¹⁷

3 Results Phillips, first American physician to report (1936)⁴ on chrysotherapy for rheumatoid arthritis, originally considered it of doubtful value, having since reduced dosage to lessen toxicity, he⁴⁵⁴ now regards it as reasonably safe and the only remedy which will notably improve sedimentation rates. He gave no detailed results, but cited an excellent response in a representative case

Ninety cases were divided by Ellman, Lawrence and Thorold into three equal groups in group 1 solganol B was given intramuscularly in "large doses" (200 mg weekly), in group 2 in "small doses" (100 mg weekly), in group 3, the control group, weekly injections of sterile almond oil were given. Treatment was continued for nine months, two courses were given, separated by an interval of six weeks. In giving results the term "rendered inactive" was defined as the patient being relieved of all subjective pain, if limitations of motion were present they were painless and sedimentation rates became normal. Results were as follows in the three groups of cases respectively disease was "rendered inactive" in 47, 27 and 3 per cent, "improved" in 14, 20 and 22 per cent, condition was unaltered in 2, 1 and 6 per cent, worse in 0, 1 and 1 per cent, there was measurable reduction in articular swelling in 66, 59 and 32 per cent, sedimentation rates became normal in 77, 37 and 13 per cent. Toxic reactions occurred in groups 1 and 2 respectively thus stomatitis in eight cases and one case, dermatitis in eight and five cases, agranulocytosis (fatal) in one case in group 1, jaundice in one case in group 1. In summary "large doses" produced many more good results and also more toxic reactions than did small doses, although 25 per cent of the controls improved, no consistent or notable effect on symptoms or sedimentation rates resulted from injections of almond oil

Results at the Brooklyn Hospital were reviewed by Tarsy. A previous series of cases was treated by his colleague, McKenna (1936)³⁰⁰. Not noted in our Fourth Review, details are given now. Fifty-two patients each received three courses of myochrysine, 22 gm each course [a rather high dose—Ed.], with an interval of six weeks between courses. More than 50 per cent of the patients developed toxic reactions, but "startling clinical improvement" was noted by the 25 patients able to tolerate the gold. Despite good results McKenna concluded (1936) that chrysotherapy was hazardous, often helpful but not curative and not safe enough for general use. De-

terminated to use smaller doses than McKenna, Tarsy reopened the subject, giving to 22 patients (including five with rheumatoid spondylitis) three to five courses of gold salts of 1 gm each (weekly doses generally 50 mg, occasionally 25 mg) "Great improvement" was noted by 12 (55 per cent) Tarsy considered gold as "one of the most valuable agents for this disease, "very toxic but one which may achieve brilliant results"

Myochrysine has been used by Cecil in "over 200 cases", his early results were "discouraging", recent results have been more impressive [No details given—Ed] He noted "a few remarkable recoveries" and many other cases in which "improvement was quite striking," especially in early cases In two cases German and King noted good but not dramatic results Sherwood who used gold sodium thiosulfate in small doses (10 mg not oftener than twice a week) considered gold useful in chronic cases, but symptomatically ineffective in "very acute cases" with leukocytosis and in relatively quiescent cases with normal sedimentation rates [No details given—Ed] Results (not detailed) in 51 cases of Margolis and Eisenstein were "very satisfactory"

4 Dosage Secher continued to use large doses, much larger than others, he gave single doses of sanocrysin of from 25 to 100 centigrams (250 to 1000 mg) Maximal single doses were 100 and 200 mg of solganol B given by Ellman, Lawrence and Thorold, 100 mg of myochrysine by Cecil Despite the better results from large doses the tendency to use smaller doses to avoid reactions is increasing Thus Sherwood gave a maximal dose of only 10 mg of gold sodium thiosulfate twice a week, Phillips gave an initial injection of 10 mg (myochrysine), then 11 injections of 25 mg each as one course, he gave two or three more courses, each a month apart

5 Toxic Reactions These can occur after only one dose or not until some time after the last dose^{17, 501} The common toxic reactions (as given in previous Reviews) were listed^{17, 209} Most toxic reactions appear only after sedimentation rates become normal according to Ellman, Lawrence and Thorold in 96 per cent of their 25 cases of gold toxemia the reactions came then "It is remarkable how often dermatitis and stomatitis appear if injections [especially of the larger doses] are continued after the sedimentation rate has become normal" [This is not our experience—Ed] In addition to the already mentioned toxic reactions noted by them (which included one fatal case of agranulocytosis) they frequently noted transient mild albuminuria without other signs of nephritis Increased joint pain was often noted but does not warrant interruption of treatment⁵⁰⁴ Sherwood^{503, 504} considered hematuria a rare toxic reaction usually seen only in spondylitis, three of the four cases in which he had noted it were cases of spondylitis Exfoliative dermatitis occurred in three cases (severe in two) of Cecil's 200 or more cases, there were no deaths and no blood dyscrasias Two severe cases of enteritis (one fatal, one not) from gold were reported A woman, 47 years old, received, within three weeks, only a few intravenous injections of gold sodium thiosulfate (total 200 mg), fatal ulcerative enteritis occurred, Anderson and Palmer reported the necropsy data with analyses of the gold content of various tissues This case resembled the fatal case of Goldhammer (1935) Severe, nonfatal colitis, necessitating 6 months of treatment, affected a woman 32 years old, given nine injections (once weekly) of gold sodium thiosulfate, total dosage was only 310 mg (Kelly)

In more than 50 per cent of McKenna's 52 cases^{399, 505} toxic reactions occurred transient mild albuminuria without other evidence of nephritis occurred frequently, mild hepatitis with jaundice, in one case, febrile epistaxis, severe in two cases, mild in six or eight, corneal ulcers, in six cases, exfoliative dermatitis, in three cases, milder dermatitis often, fatal cerebral thrombosis, in one case after six injections, each of 50 mg of myochrysine Among his own 22 cases Tarsy noted the following

toxic reactions exfoliative dermatitis in four cases, thrombocytopenia (platelets 120,000) in one, eczematous or maculate dermatitis in two, a fatal cerebral accident in one case six weeks after the last injection and after the onset of a scarlatiniform rash

Most of the rheumatologists who answered the questionnaire of Margolis and Eisenstein were afraid of chrysotherapy. They reported mild toxic reactions, in 10 per cent, moderately severe in 25 per cent, fatal in 0.8 per cent of cases. One instance of fatal aplastic anemia was noted. One informant wrote, "Used it once, never again." Some physicians were more enthusiastic, but the majority considered chrysotherapy "promising but at present dangerous", "should not yet be generally adopted", "not sufficient in results to justify the risk."

6 Treatment of Toxic Reactions There is no specific antidote, treatment is symptomatic. Sherwood considered time the only remedy for the dermatitis. Purpura results from thrombocytopenia, for the latter Sherwood stopped injecting gold and gave liver extract and vitamin C daily until platelet counts became normal. Dextrose and intravenous injections of sodium thiosulfate, the use of liver extract, calcium gluconate and vitamins A, B, and C were recommended by some but regarded as of questionable value by others.

[We know of no satisfactory treatment for toxic reactions—Ed]

7 Prevention of Toxicity Secher again⁴⁹⁸ advised the use of large doses of vitamins A, B and C, since using them he has had no cases of thrombocytopenia and has reduced the incidence of erythema. According to him much "gold toxemia" results not from gold but from ascorbic acid deficiency, not from metallic poison but from "liberated toxins." [Secher gave no statistics and few examples of the value of vitamins. The doses of ascorbic acid given were not noted—Ed] Tarsy's prophylactic regimen included viosterol 15 drops daily, calcium gluconate 1 drachm twice a day and intravenous injections of 2 cc of ascorbic acid. If itching or vertigo appears, use of gold should be discontinued. [Despite his scheme, toxic reactions affected 37 per cent of his patients, one case fatally—Ed] In the presence of bleeding gums or purpura Sherwood stopped gold injections permanently, he considered vitamin C somewhat protective. Liver extract was considered by MacKee and Astrachan of some value in preventing intolerance to heavy metals, including gold.

[Only one instance of chrysotherapy was specifically mentioned. We know of no remedy which will prevent toxic reactions—Ed]

Patients under chrysotherapy should have examinations of mouth, skin, urine and blood cells each week, platelet counts and estimations of nonprotein nitrogen of blood every three to four weeks, at first signs of a reaction treatment should be stopped for a month, then resumed with smaller doses⁵⁰⁶. Because the toxic reactions observed by them came almost exclusively when sedimentation rates became normal, Ellman, Lawrence and Thorold stopped injections when rates fell below 12 mm, waited three or four weeks, then gave smaller doses (about 20 mg weekly). If pruritus occurs, gold therapy should be stopped at once, or exfoliative dermatitis may appear⁵⁰⁸. The best prophylactic is the use of small doses of gold, according to Sherwood⁵⁰¹, by giving not more than 10 mg once or twice a week he obtained "very beneficial results," no fatalities and only one reaction necessitating hospitalization.

8 Mode of Action To study the pharmacology of gold salts, a new method for quantitating gold in urine and blood with the Evelyn photo-electric colorimeter was reported⁵⁰⁴. Some regard gold as a catalyst⁵⁰⁵. Gold sodium thiomalate possesses marked bacteriostatic effects against experimental hemolytic streptococcal infections in mice, a dose of 2 mg given subcutaneously protected most animals injected with 1,000 times the lethal dose of culture (Dawson and Hobby). Sabin and Warren compared the bactericidal effects of myochrysin and a new compound, calcium myochrysin, on experimental arthritis in mice inoculated with pleuropneumonia organisms.

[How gold salts work in rheumatoid arthritis is not known—Ed]

9 *Conclusions on Chrysotherapy* Some current conclusions follow. Despite its dangers, it forms "the best means at our disposal for the treatment of chronic rheumatism", such is the Italian view⁴⁸⁴. It should be used "as a routine for all cases in which the disease shows evidence of a progressive course", the most suitable dose is still debatable¹⁷⁵. Although early high hopes have not been fully realized, this remedy is "of greater value than any other single measure"²⁰⁵. But German and King called it "too dangerous for general use" and Pemberton said, "*Gold is intoxicating* and may cause serious reactions. Use it last, if at all". Westcott and other associates of Pemberton regard gold with "waning enthusiasm," a remedy to be used only in research clinics. Still others took an intermediate position. "The seriousness of the disease justifies its cautious use"²⁰⁵. According to Cecil, chrysotherapy marks an important advance, it is a "dangerous agent," but "in the hands of an experienced therapist it can be used with considerable benefit". It is "effective but dangerous" according to Sherwood, gold is a lethal drug which easily can cure the disease but kill the patient, the larger the dose, the quicker the result, and the higher the mortality rate.

[We approve the opinion of Osgood that "gold therapy has its seeming triumphs and its possible disasters. If it be carefully controlled it has a better chance to survive than either sulfur or vaccine therapy". But Osgood reminded us of the end results, without the use of gold, reported by Kahlmeter⁴ three years after their dismissal from the hospital 60 per cent of Kahlmeter's patients were back at work. No final evaluation of chrysotherapy is yet possible.—Ed.]

10 *New, Relatively Nontoxic Gold Compounds* Convinced that gold salts are beneficial, workers are seeking some new nontoxic gold compound. A new and presumably "comparatively nontoxic" gold compound, auro-sulfide (Hille), an aqueous solution of colloidal gold sulfide, was given by Driscoll and Markson in varying doses to 51 patients with rheumatoid arthritis. 41 per cent were "definitely improved" (as were 39 per cent of 49 patients with osteo-arthritis). Toxic reactions (nausea and vomiting) occurred in only 2 per cent of their cases.

[These results will have to be reevaluated in the light of the recent report of Freyberg, Block and Levey who noted that the absorption and utilization of colloidal gold (auro-sulfide) is different from that of crystalline compounds (myochrysine, sanocrysin). When colloidal gold was used, the average amounts of gold in plasma and urine were small, even though much more gold was given than when the crystalline forms were used. This may account for the lower toxicity of colloidal gold, also "therapeutic failures are to be expected in those persons whose plasma gold values are very small". It will be remembered that Forestier³ (1935) stated that colloidal gold is ineffective.

In this and in previous Reviews we have reported the doses of gold as stated by the various writers, these doses have almost always referred to the gold salts and not the actual gold content. Myochrysine (gold sodium thiomalate) contains 505 mg of gold and 82 mg of sulfur per gram, that is myochrysine is about 50 per cent gold by weight. When 100 mg of the gold salt which is commercially sold as myochrysine are

given, really only about 50 mg of gold are given. Sanocrysin (gold sodium thiosulfate) is 37 per cent gold by weight, it contains 374 mg of gold and 240 mg of sulfur per gram. The new gold compound, auro-sulfide (colloidal gold sulfide—Hille) is 87 per cent gold by weight, a 0.5 per cent solution contains 4.35 mg gold and 0.65 mg sulfur per cubic centimeter (i.e., 870 mg of gold and 130 mg of sulfur per gram). Thus in comparing the relative toxicity and effectiveness of the various gold compounds it should be realized that some compounds contain only from a half to a third as much gold as others. For comparative purposes it would be best if investigators reported doses in actual gold content. For the present, however, we will continue to report doses as stated in the original references—Ed.]

More promising is the preliminary report of Sabin and Warren who from a study of comparative toxicity of various gold compounds found that their toxicity (as measured by lethal effect on mice) and their therapeutic value (as measured by their effect on experimental arthritis from pleuropneumonia organisms), were functions of different attributes of the gold compounds. They noted that although "colloidal preparations of gold or of gold sulfide were therapeutically inert," a distinct, though delayed, curative effect followed the use of an insoluble compound, calcium aurothioglycomalate. In mice "the margin of complete safety" was "at least 100 times greater" for this compound than for myochrysine, and the new compound was "about ten times more effective therapeutically" than the latter.

[Clinical and further experimental studies with this compound will be awaited with great interest—Ed.]

Vasodilators *Histamine, Choline* Histamine diphosphate dilution (1 to 1000) was given subcutaneously (0.1 to 0.6 cc) by Muether to 10 patients with rheumatoid arthritis; seven noted increased mobility and diminution of pain. Histamine given subcutaneously is as effective as when given by iontophoresis and much more effective than when applied in ointments. "Histamine will not cure arthritis, it is at best an adjunct." Ointments containing histamine hydrochloride dilate capillaries but constrict arterioles according to Cohen and Rosen; ointments of acetyl-beta-methylcholine chloride dilate both capillaries and arterioles. The latter ointment gave "some measure of relief" to 96 patients with "arthritic pain resulting from circulatory disturbances."

[Type of arthritis not stated. These patients received other treatment besides the vasodilators. Results do not impress us—Ed.]

Sulfanilamide This drug is valueless.

Bile Salts, Liver Extracts, Etc No practical method has been found to reproduce the effect of spontaneous jaundice by giving bile salts, bilirubin, liver extracts, alone or in combination. Hench²⁵⁰ reviewed his own attempts and those of others. The introduction of bile salts by iontophoresis produced no effect, other than local hyperemia, on "several patients with rheumatoid arthritis (Westcott)." Cecil¹⁰² was unable to confirm the impression of Davis¹⁵¹ that large doses of crude liver extract affected rheumatoid arthritis favorably.

Rest and Motion "Rest is the hardest but the most important medicine to take"⁵⁰². Systemic rest is almost a *sine qua non* for seriously ill arthritic patients. Preferably this means putting a patient to bed in a hospital. In some cases this is all that is necessary.⁴¹⁷ When rest in bed is

impossible the patient should regulate his activities to permit as much rest as possible. But "body-rest in bed" must be combined with "joint-motion in bed" to prevent contractures by moving each joint through its full range of motion once or more daily.²⁷²

Physical Therapy A number of general articles on the indications, contra-indications, methods of application and latest developments of various forms of physical therapy appeared^{103, 207, 280, 334, 336, 387, 389, 341, 387, 404, 502} Especially useful was one by Kiusen.⁷¹⁰ Physicians are increasingly stressing the importance of teaching patients methods of home physical therapy "self help under sound direction"^{252, 260, 710}

Simple methods applicable for home use were described^{258, 330} A cheap heating lamp used 365 days a year is of far greater value than some elaborate form of physical therapy which the patient can afford only for a few days or weeks.¹⁰⁸ "I am convinced from long experience that, when patients are properly instructed concerning home massage, much more good than harm will result even though the amateur masseuse cannot hope to approach the skill of the trained technician."³⁸⁹ Copeman described methods, used by him in the British Expeditionary Force, to provide physical therapy in war hospitals not equipped with electricity

[They are mentioned later under "Physical therapy and War"—Ed.]

Indications for short and long wave diathermy were discussed.¹⁶⁹ Diathermy provides the most effective source of deep local heat.^{336, 340} Diathermy may aggravate acute arthritis or bursitis unless given in small doses.^{155, 615, 616} In the treatment of bursae and the more superficial joints Kovacs³³³ preferred long wave to short wave diathermy. Some who considered diathermy "useless" for rheumatoid arthritis^{23, 82} preferred galvanism.⁸²

The newer technic of contrast baths,³³⁹ indications for paraffin baths,^{335, 387} various forms of light therapy^{341, 387} and hydrotherapy^{168, 392} were described. Ultraviolet therapy is contraindicated in presence of fever.³⁸⁷ The distinct advantages of underwater therapy were stressed.^{192, 197, 345, 466}

Spa therapy received constructive criticism. There are more than 300 health resorts in the United States, but they have not had the full support of the medical profession for various reasons, chiefly because of objectionable forms of publicity and frequent lack of competent medical direction,^{335, 392} also because of "absurd claims made by hotel managers, bath attendants and even medical directors for virtues of their particular mineral waters."⁶¹³ "Quackery and incompetent diagnosis and treatment are almost habitual at these places" (Wyman). Kovacs³³³ recommended more effective cooperation between spa organizations and the medical profession to raise spas to the high standards of our hospital system, insuring dependable skilled care for rich and poor. Managed properly, spas have many advantages for rheumatic patients.⁵²⁰

Medical schools and hospitals should do more to train students, internes and graduate physicians how best to utilize physical therapy.¹⁸⁶ Approved schools for physical therapy technicians were listed.¹⁸⁷ The University of Minnesota has instituted graduate teaching and continuation study in physical therapy.^{426, 427}

Climate There is not enough certainty as to the influence of climate to justify families to make considerable sacrifices of convenience or of earning power to secure a change of climate (Horder).²⁸⁰

Occupational Therapy Several reports stressed the importance of occupational therapy.^{37, 144, 269, 304, 458} Types of exercises suitable for the vari-

ous stages of arthritis and for the specific joints affected were described and specifically grouped by Pattee. Recently the British Army adopted occupational therapy as an approved method of treatment for rheumatic and allied conditions.²⁸⁰ Approved American schools of occupational therapy were listed.¹⁸⁸

Roentgen Therapy Of eight patients given roentgen therapy in "relatively large doses" by Ochsner and Mumford one obtained complete relief, four, "great" relief of pain and stiffness, the appearance of relief was sometimes delayed several weeks. Of 39 cases of "arthritis" in which roentgen therapy was given, Weinberg noted "complete relief" in 13, "improvement" in 26.

[These studies were not controlled, in the second study no attempt was made to clarify the types of "arthritis" treated. More recent, well controlled studies^{522, 523} lead to the conclusion that roentgen therapy, although perhaps valuable for rheumatoid spondylitis, is of little more than psychotherapeutic value in rheumatoid arthritis of peripheral joints.—Ed.]

Inhalation of Carbon Dioxide A "transient, small but significant" decrease in stiffness was noted by 10 patients with rheumatoid arthritis (but not by 10 with osteo-arthritis or fibrositis) who inhaled 10 to 15 per cent carbon dioxide in oxygen for two to five minutes.³⁰⁵

Fever Therapy Few physicians are still using fever therapy. It was considered "helpful in selected cases,"¹⁸⁵ "a reliable measure" when used with other measures⁵¹³ and "encouraging" in its results.⁵⁸⁰ [How weak in praise is such a remark as results were "encouraging." Swallowing a lot of disappointment, the investigator thereby sadly makes the best of very little.—Ed.] Others regarded fever therapy as of little value.^{231, 236, 258} For 75 per cent of 114 patients treated by Solomon and Stecher immediate results were quite satisfactory, but final results, assessed on follow-up, were disappointing: condition of 10 per cent was "improved," of 82 per cent, unchanged, of 8 per cent, worse. Thirteen patients of Margolis and Eisenstein received only very transient relief. Of 57 physicians whom they questioned the majority had abandoned this remedy for rheumatoid arthritis, two fatalities and two near fatalities were noted.

Splenectomy Recent reports have given results of splenectomy in four cases of rheumatoid arthritis, splenomegaly, adenopathy, leukocytosis or leukopenia, with or without hepatomegaly. One patient noted marked improvement maintained at least five months (Hanihan and Miller,¹ 1932), another noted only transient improvement (Craven,² 1934), both patients died within 18 months after splenectomy (Fitz,³ 1935). A third patient obtained a "marked" immediate improvement but died of pneumonia 35 days after operation (Loeper, Lemaire and Patel, 1937). The fourth patient noted a gradual but marked improvement (Villaret et al., 1937).

Splenectomy has been done in three additional cases by Bach and Savage with "marked clinical improvement" in two, no postoperative improvement but gradual quiescence of arthritis in the third. Brief reports of the three cases follow.

A female, aged 18 years, had splenomegaly, adenopathy, anemia and leukocytosis. After splenectomy improvement was gradual. A youth, aged 18 years, had adenopathy and anemia but no apparent splenomegaly. Improvement after splenectomy was not notable but 10 months later the arthritis was becoming quiescent. A woman, aged 29 years, had severe rheumatoid arthritis but no splenomegaly, adenopathy or anemia.

After splenectomy a slow steady improvement occurred. In the second and third cases the spleen was found at operation to be twice normal size. Splenic amyloidosis was present in two of the three cases.

[We would hardly call the improvement in these cases "marked." Results in these seven cases do not encourage physicians to advise splenectomy and we know of no rationale for the procedure—Ed.]

Non-surgical Orthopedic Methods. Most deformities could be prevented if patients had the services of both physician and orthopedist from the onset of their disease. Arthritic patients are prone to adopt the "comfortable position", too often this leads to disaster⁵⁵⁶. The common deformities and optimal positions for joints with impending deformities were listed^{86, 556}. The simple technic for proper splinting was described^{30, 576}. A simple device whereby patients may apply forced flexion to knees was reported¹⁷⁴. Some¹¹⁴ favored the use of wedged casts to correct flexed knees and reserved capsulotomy for subluxation of knees⁵⁰.

Technic for manipulation (without anesthesia) of spine³² and peripheral joints⁶⁰⁰ was described.

Surgical Orthopedic Measures. Aspiration of effusions may reduce intraarticular pressure and prevent small subchondral herniations of debris¹⁹⁹. Injections of oxygen into arthritic joints were considered useful by Henson¹⁰² in preventing adhesions and relieving pain. [Details were too meager to prove the writer's point—Ed.] Manipulation of joints under anesthesia was considered "dangerous" by some,⁸⁶ useful by others⁶⁰⁰.

Indications and contraindications for various orthopedic measures to correct deformities were again discussed^{30, 452}.

Synovectomy, performed by Caruthers 34 times on 28 patients with chronic arthritis, chiefly of the rheumatoid type, gave these results: "very satisfactory" in 22, "fair" in two, improvement in six, failure in four. Reviewing 10 years' experience Speed and Smith concluded that best results from *arthroplasty* were obtained by patients aged 18 to 30 years, and when arthroplasty of hips, knees, elbows or jaws was performed. Preliminary results were satisfactory in two cases in which Speed performed an arthroplasty of hip with insertion of vitallium cap. Results with this procedure on hips have been good enough to warrant further trial, final evaluation cannot be made yet⁵⁸⁰. Campbell⁹² adopted this procedure (interposition of vitallium plate after arthroplasty) in two cases of ankylosed knees (from acute pyogenic arthritis) with disappointing results. Transplantation of tibial tubercle was recommended by Preston as a supplement to posterior capsulotomy for flexed knees: this permits immediate full active extension of knees. Royle described an operation for *arthrodesis* of knee joints "used for 15 years without a failure", femur and tibia unite in 12 weeks.

[Number of patients treated not given—Ed.]

Psychotherapy. Consciously or unconsciously applied, psychotherapy is essential to the successful handling of rheumatoid patients, who are, as a class, fretful, unreasonable, introspective and without confidence in themselves or their physician. Many lack the urge to get well. Institutional or spa therapy gains much of its success because patients are removed from unhappy surroundings and given optimal rest and care²⁰⁶. These patients

are peculiarly amenable to suggestion Of 33 rheumatoid patients given injections of physiologic saline solution by Sidel and Abrams 72 per cent felt "improved" Similar injections were given as psychotherapy by Phillips in selected cases

Institutional Care The advantages of institutional care were again described ⁶¹³

Integration and Coordination of Treatment So many remedies are recommended for rheumatoid arthritis that physicians find it difficult to decide what to try first and what to leave until last Two writers ^{258, 447} listed their therapeutic choices, gave opinions as to the relative value of each remedy and defined their programs I, II, etc The fact that their selections did not always agree is further evidence that the treatment of this disease cannot be standardized yet, the fact that they (and others) have agreed on the value of certain remedies indicates that there is a basic program of therapy of the value of which there is little doubt

Prognosis End Results No new statistics on end results were published Such statistics are difficult to collect, largely because of the unpredictable nature of the disease Remissions and exacerbations occur most irregularly, many remissions are long enough to be interpreted wrongly as "cures" unless follow-up is carefully made ⁵⁹⁶ One long-time student of the disease ⁴⁸⁵ would only say, "we may expect a certain number of cures, a certain number of remissions, a lesser number of exacerbations and an almost negligible number of patients who will not admit that our care has lightened their load" Unfortunately we badly need more definite information on end results, a few statistics previously given herein were repeated by Snyder

Failures may be the fault, not of the patient or his disease, but of the physician himself who may (1) fail to make a complete diagnosis, (2) not trust his patients' ability to evaluate therapy ("when the patient comes in and tells you that he has been worse since his last treatment, surely that treatment should be repeated with utmost caution") or (3) not be thorough in treatment (Sherwood) ⁵⁰³ Such failures are inexcusable These patients deserve the best their physicians can provide Although some are fretful and wearisome, "the courage, patience and fortitude of the arthritic exceeds that of any other patient afflicted with a chronic disabling disease It is hard to understand how they can bear the pain, disappointments, and long periods of inactivity in silence or more usually with smiles Many times it is the courage of the patient that has kept his physician from abandoning all hope of improvement" (Wyman)

STILL'S DISEASE AND "FELTY'S SYNDROME"

[Readers will be interested to know that Sir Frederick Still died just recently in London, aged 73 years —Ed]

In Still's disease (juvenile rheumatoid arthritis with splenomegaly, adenopathy, and anemia) the pathologic reactions in lymph nodes and spleen are not specific ⁴⁴ Blood cultures from two children who had febrile Still's disease revealed no pleuropneumonia organisms ¹⁸⁷ Results of fever therapy

in two cases of Still's disease were "excellent" in one, less notable in one²⁶⁸ Ishmael used fever therapy plus autohemotherapy in 11 cases, "complete remissions" resulted in nine

[These results are so unusual that we are anxious to know what a late follow-up will show—Ed]

Relation of "Felty's Syndrome" to Still's Disease Ravenna cited an Italian report of two cases of "Felty's syndrome" (leukopenic splenomegaly with polyarthritis) and added that most Italian authors do not recognize the autonomy of this syndrome "which has the same characteristics as Still's disease". A similar conclusion was reached by Curtis and Pollard who compared four cases of "Felty's syndrome" (rheumatoid arthritis of adults with splenomegaly, adenopathy, anemia and leukopenia) with four cases of rheumatoid arthritis, splenomegaly and leukocytosis (not leukopenia) and four cases of rheumatoid arthritis without splenomegaly or leukopenia

In 11 of these 12 cases biopsies of the skin and calf muscle were made, biopsy of the lymph nodes was made in one, examination of spleen, lymph nodes, bone marrow and muscle after death was made in one case to determine whether or not the disease was generalized and whether Felty's syndrome was a clinical entity or just an expected complex of the disease. Patients were adults aged 27 to 67 years with articular changes characteristic of rheumatoid arthritis. Pathologic reactions in spleen, lymph nodes and bone marrow were nonspecific, "the result of a chronic infection". Reactions in skin and muscle of calf were essentially the same in the three groups studied: atrophy of epithelium, fibrosis of corium, increase in interstitial nuclei of muscle fibers, small perivascular infiltrations throughout corium and muscle—an "angiomysitis" indicating a generalized infectious process. Since the pathologic reactions in the cases of "Felty's syndrome" were similar to those in which only rheumatoid arthritis was present or in which splenomegaly was *not* associated with leukopenia, Curtis and Pollard concluded that the likelihood of the various features (splenomegaly, adenitis, leukopenia or leukocytosis) occurring with rheumatoid arthritis is merely a matter of chance. "There is therefore no justification for the segregation of these cases, the use of the term 'Felty's syndrome' should be discontinued" [We share this opinion—Ed]. They concluded that Felty correctly interpreted the syndrome, the several features being manifestations of one pathologic process caused by a noxa (the unknown cause of rheumatoid arthritis) which simultaneously affects joints, spleen and circulating leukocytes.

Four cases of "febrile hepatosplenomegaly with arthritis" were described²⁶⁹ Splenectomy reputedly improved two of three patients with adult Still's disease ("Felty's syndrome") seen by Bach and Savage

OSTEO-ARTHRITIS DEGENERATIVE JOINT DISEASE

"Osteo-arthritis" (or "degenerative joint disease") refers, not to a specific disease but to a type of cartilaginous degeneration accompanied by hypertrophic osseous changes. "Primary osteo-arthritis" (primary degenerative joint disease) is that form which develops insidiously and more or less spontaneously in persons more than 40 years of age. "Secondary osteo-arthritis" (secondary degenerative joint disease) refers to hypertrophic osseous changes in joints incident to trauma (acute, occupational, static, chronic trauma resulting from congenital or acquired joint malformation, etc.) or as a secondary (late) manifestation of another type of arthritis (rheumatoid, gouty, suppurative, etc.)

PRIMARY OSTEO-ARTHRITIS (HYPERTROPHIC, SENESCENT, DEGENERATIVE ARTHRITIS)

Incidence To obtain the incidence of Heberden's nodes Stecher examined 6,913 subjects Traumatic nodes were rare in women, common in men even at early ages The incidence in physicians was low in all age groups The percentage incidence in different age groups was as follows (table 3)

TABLE III
Percentage Incidence of Heberden's Nodes in Various Age Groups (Stecher)

	Age, yrs								
	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90+
2233 white males	1 7	8 6	8 8	11 4	19 1	28 6	32 0	29 5	66 7
2187 white females		0 2	3 6	6 6	15 4	27 5	40 8	32 3	60 0
846 negro men		8 7	6 4	10 5	13 0	21 3	18 8		
1117 negro women		0 0	2 6	2 7	4 0	16 7	25 0	50 0	
530 white physicians		1 9	4 8	4 8	13 7	14 7	14 3		

[“Traumatic nodes” (e.g., “baseball fingers”) represent secondary, not primary osteo-arthritis Many of the nodes in the earlier age groups probably represented secondary osteo-arthritis But primary Heberden's nodes may (rarely) affect young persons, even children”—Ed]

Clinical Data The usual clinical features of osteo-arthritis were reviewed^{45, 69, 258, 261, 285, 538, 573} Thomson noted an engraving of a woman aged 104 years with osteo-arthritic hands

Hypertrophic changes in terminal phalangeal joints were classified into three stages (1) enlargement, (2) enlargement and flexion and (3) enlargement, flexion and deviation (Stecher) Enlargement is apparent, sometimes as two small nodules on the dorsolateral aspect of the terminal joint, but more often as a definite ridge across the dorsum At times the nodes are soft or even fluctuant Thumbs are comparatively immune to Heberden's nodes, involvement of toes is not observed Osteo-arthritis of knees commonly affects patellae. palpation during motion elicits crepitation beneath the patella, passive motion of that bone is often painful, patients usually locate pain and tenderness in the anterior part of the knee about the patella (Haggart). Pleves believes that osteo-arthritis of a hip with much formation of new bone is less painful than when formation of new bone is minimal The presence of slight or moderate osteo-arthritis in cases of traumatic synovitis, ligamentous or muscular strain is often little more than coincidental Unless hypertrophic changes are sufficiently marked to result in disordered joint mechanism, disability should not be attributed to such changes The frequent occurrence of roentgenologic evidences of symptomless osteo-arthritis was noted^{177, 502}, its medicolegal importance was stressed⁵²⁹

Roentgenograms Usual features were described ^{101, 520} According to Haggart roentgenograms of knees in osteo-arthritis consistently reveal degenerative changes about the patella although arthritic changes may not be visible in other parts of the joint Enlargement of the patella, exostoses on the proximal and distal ends of bone and narrowing of joint space are frequent findings Roentgenograms rarely give an accurate idea of the degree of cartilage degeneration and erosion which is actually found at operation Loss of joint space, subchondral osteosclerosis, and osteophytes are the three cardinal signs of osteo-arthritis (Plewes)

Pathology Pathologic features were reviewed ^{233, 285 520, 538} The most common operative findings in a severely involved knee are marked synovial hyperplasia, erosion and degeneration of articular cartilage particularly over femoral condyles, thinning and fibrillation of patellar cartilage, hypertrophy of patella and exposure with eburnation of the subchondral bone (Haggart) Degeneration of femoral cartilage was consistently most pronounced in the patellar groove

[Synovial hyperplasia is not a characteristic feature in pure osteo-arthritis, when present it probably signifies the presence of a mixed type of arthritis—Ed]

Laboratory Data Sedimentation rates are often elevated ^{484, 500} Formol-gel reactions are occasionally positive ⁴⁹⁸ [The abnormal sedimentation rates and formol-gel reactions are probably caused by factors other than the osteo-arthritis—Ed] Blood plasma may contain increased amounts of substances which reduce chromic acid ¹⁴⁷

Etiology 1 *Factors of Tissue Senescence and Trauma* Cartilage degeneration from increasing age, "wear and tear," and repeated or severe single trauma were considered most important ^{212, 283, 285, 455, 538} In 50 per cent of Plewes' cases of unilateral painful hips there was roentgenographic evidence of symptomless osteo-arthritis in the opposite hip He assumed that the "wear and tear" of daily life produced symptomless changes in both hips, on the injured side trauma accelerated the process to the point of pain

2 *Factor of Impaired Circulation* This was discussed but no new data were presented ^{212, 453, 538}

3 *Factor of Endocrine Dysfunction* Hoskins described a hypothyroid and a menopausal type of osteo-arthritis but failed to present convincing data to support such classification

[Claims made by some that endocrine dysfunction plays an etiologic rôle in osteo-arthritis are based on vague clinical impressions and are not supported by adequate biochemical evidence—Ed]

4 *Factor of Altered Metabolism* The belief that an abnormal sulfur metabolism exists in osteo-arthritis has been based on the inconsistent findings of a lowered cystine content in finger nails, ²⁸⁵ a reduced sulfur content of articular cartilage ¹⁰⁰ and the frequent excretion of free indole in the urine of arthritic patients ²⁰⁰ But Freyberg, Block and Fromer could not demonstrate important abnormalities in sulfur excretion of such patients

5 Factor of Infection Infected foci are often present^{22, 84, 444} But Gibson²¹² stated that osteo-arthritis must not be considered an infectious process the recognition of this fact may "permit of many teeth being retained, even of tonsils being spared and sinuses remaining unmolested"
[We agree—Ed]

Precipitin reactions to hemolytic streptococci are usually negative⁷² and antistreptolysin titers are normal⁷⁰

Treatment The advice "keep your joints on the move or they will become completely stiff" was condemned⁴⁵⁵ Complete rest of a hip in a plaster spica is often followed by increased mobility⁴⁵⁵ It is important to reassure the patient that he has not a seriously crippling form of arthritis The value of reduction for obese patients was recognized^{201, 285}

Giving average daily doses of 300,000 U S P units of vitamin D, Snyder and Squires obtained good results in 6 of 11 cases of osteo-arthritis Sulfur therapy had its advocates,^{100, 285} but Freyberg, Block and Fromer could find "no biochemical or metabolic indication of a need for, or benefit from, sulfur medication in the treatment of arthritis" Lactalbumin was given intradermally by Strauss Colloidal gold was considered valuable for osteo-arthritis by Driscoll and Maikson [Practically nobody else takes this view—Ed] Fletcher¹⁹¹ claimed that in 75 per cent of his cases "great improvement" occurred after treatment with intramuscular injections of chaulmoogra oil Bee venom was used by some^{216, 415} Cobra venom gave slight to moderate relief of pain in 17 of 23 cases⁵⁴⁰ [We have very little faith in the value of vitamin D, sulfur, foreign proteins, chaulmoogra oil, and bee or cobra venom for osteo-arthritis—Ed] As evidence of the psychotherapeutic value of "injections" 86 per cent of 64 osteo-arthritic patients given injections of physiologic saline solution by Sidel and Abrams claimed to be "improved" Theelin was considered of value in relieving the pain and swelling of Heberden's nodes⁵⁰³

[No data were given to support this idea—Ed]

Many considered physiotherapy useful^{82, 102, 197, 387, 379} but others considered it rarely more than of temporary benefit in osteo-arthritis of hip⁴⁵⁵ and knee^{169, 233} Roentgen therapy for relief of pain was approved by some^{129, 155, 572} Twelve of 15 patients with osteo-arthritis of the hips received "immediate good results" from roentgen therapy (Plewes) Weinberg reported excellent results in a large group of patients with spinal or peripheral osteo-arthritis Treatment was given directly over involved regions in doses of 100 to 150 r two to three times weekly for 3 to 12 treatments Ochsner and Mumford obtained relief of pain in 87 per cent of cases (rheumatoid and osteo-arthritis)

[These appraisals are more enthusiastic than those of many others—Ed]

Local injections of procaine to relieve pain were recommended¹⁰² Results from manipulation under anesthesia for osteo-arthritis of hips are usually short lived^{201, 455} Bone drilling was not recommended by some,^{212, 157} but others obtained relief of pain therewith in 36 per cent of selected cases⁴⁶⁰ Reshaping the head of the femur is often followed by instability of the joint, and was considered useless Subtrochanteric osteotomy was not successful^{201, 175} Arthrodesis relieves pain in many cases and was recommended when one hip was involved The use of the vitallium cap in connection with arthroplasty of hips was enthusiastically approved^{212, 710, 711} The operation is

usually recommended for adults, but Speed believes the procedure may be safely used for adolescents more than 16 years of age whose acetabula are fully ossified. Arthroplasty of the ankle was not recommended because the resulting articulation is often painful and may cause more disability than that incident to ankylosis (Speed and Smith). Synovectomy was considered valuable for the relief of "painful arthritic knees" (Carruthers). [Description of the types of arthritis referred to was vague.—Ed.] Haggart advised operative removal of all abnormalities (in so far as is feasible) in cases of advanced osteoarthritis of knees. Combined excision of the patella, synovectomy, removal of exostoses and shaving of degenerated cartilage were attended by improvement in 19 of 20 cases.

BACKBONE AND SCIATICA

General Remarks on the Causes of Backache and Sciatica For this section on backache and sciatica we reviewed more than 90 papers. Since most of the reports of 1940 on backache concerned data repetitious of material in recent Reviews we shall only cite the more significant papers. The various causes of backache and their distinction, with illustrative case reports and methods for examining backs were reviewed^{385, 392, 342, 408, 409}. The dynamic muscle-bone balance of the back was carefully studied by Carey, illustrations of his models graphically portraying this balance were published. According to Carey, muscle imbalance itself can lead to permanent structural changes in the spinal column.

The famous epigram "A woman is a constipated biped with a pain in her back" was attributed to Dr. Henry I. Prentiss⁴²⁰. It is a common practice of physicians, in cases of backache even when roentgenograms fail to show any abnormality to dispose of the complaint with the remark, "There must be a small spot of rheumatoid arthritis somewhere." This is unsound practice, according to Lang, because cases in which spinal rheumatoid arthritis is isolated and confined to one spot in the spinal column or sacro-iliac joint are rare.

Lumbosacral and Sacro-iliac Back Strain "Industrial Backache" The tendency for industrial surgeons to lump cases of backache among working men under the term "industrial backache" was deplored by Johnstone. A diagnosis of "industrial backache" (presumably related to injury) was found to be unjustified in from 70 to 80 per cent of cases so styled and in these cases no injury to account for the complaints had been experienced. In only about 30 per cent of the cases was the condition regarded as compensable because of true industrial trauma. The so-called industrial back is not primarily a problem for the orthopedist but "represents a problem in differential diagnosis for the internist."

Muscular and ligamentous strains are still considered to be the commonest causes of chronic backache^{338, 363}. Cases of transient acute backache with acute onset of pain after mild or major trauma are generally presumed (if fractures, etc. are ruled out) to result from subluxation of one of the intervertebral joints or an incomplete tear of an adhesion in periarticular tissues (Little). Despite such presumptions there is little evidence that

"adhesions" do exist and many experienced clinicians strongly doubt the presence of "subluxations" Nevertheless spinal manipulations (which can do only two things—replace displaced articular surfaces or break down adhesions) often seem to be helpful (Krusen,³⁸⁸ Little) Technic for spinal manipulation without anesthesia was described³⁸⁸ The disability of 200 patients so treated by Little was relieved in an average of four or five days

Miscellaneous Causes of Backache In current reports little, if any, new data were found on backache from urologic lesions, from gastrointestinal disease, from lesions of the pyriformis muscle No new studies on the "dorsolumbar syndrome" (first lumbar nerve neuralgia), on diseases of interspinal ligaments or on the "facet syndrome" appeared Cases of backache from pelvic lesions represent only a small fraction of cases of back pain According to Mengert⁴⁰⁸ commonest pelvic causes for backache are (1) induration and infiltration of pelvic cellular tissues with carcinoma, postpartum or postabortal phlegmon, abscesses and cellulitis, and (2) occasional endocervicitis with chronic posterior parametritis causing nagging persistent backache "Pelvic disease causing backache is well-defined, readily recognized, generally severe, acts in a direct and easily understood manner and *always produces other symptoms*"

[Italics are ours—Ed]

"Postural Backache" Criteria for this diagnosis were cited by Krusen³⁸⁸ whose treatment for severe chronic postural backache included (1) rest in bed with fracture board and hair mattress, (2) traction of four to eight pounds (1.8 to 3.6 kg) on each leg, (3) padded lumbar sling, (4) daily physical therapy including postural exercises, (5) if necessary, epidural injections, (6) "finally" manipulation under anesthesia "We have rarely noted more than temporary relief after manipulation"

Types of Back Pain and Sciatica Suitable for Manipulation of Back Manipulation without anesthesia was used by Miltner in cases of (1) backache caused by subluxation, (2) impingement and overriding of articular facets, (3) chronic myofibrositis, (4) adhesions and mild stiffness of spinal column from chronic sprain and "burned out" arthritis Jostes³⁰¹ also recommended manipulation in these and other conditions vaguely defined as "those conditions of low back-pain whose pathological background is indifferent or indeterminate so far as correct allocation of the cause of the pain is concerned" Technic was detailed^{301, 412}

Backache from Contracted Iliotibial Bands At the suggestion of Macey, Krusen³⁸⁸ treated this condition by stretching the fascia by certain forcible passive and active exercises, thus avoiding, in some cases, a painful surgical procedure (fasciotomy) "which has not often been successful" at the Mayo Clinic

Coccygodynia. Treatment recommended for this was radiant heat daily, internal massage per rectum (technic given), and the use of rubber rings if necessary, if conservative measures fail after six months of use, simple excision of the coccyx is justified (Krusen and Basom)

Spondylolisthesis Some interesting studies on the genesis and progression of this condition were reported⁴²⁰ Despite the general idea that this

dislocation gradually progresses Hitchcock was unable to find in the literature a single case in which progression of the spondylolisthesis from one examination to the next had been demonstrated roentgenographically He reported three cases of his own with roentgenographic evidence of progressive slipping of the fifth lumbar vertebra on the sacrum, trauma of delivery was held responsible

Backache from Senile Osteoporosis Black¹¹ studied 208 cases of this condition

The sex incidence was four females to one male (167 to 41) The average age of patients was 62 (minimum 45, maximum 87) years when diagnosis was first made Usual symptoms were weakness, fatigue, a dull ache over the lower back for about three years (average), then as a result of slight trauma the onset of more acute pain, at times severe enough to confine the patient to bed Pain is relieved by rest and supports, aggravated by activity, twisting, and lifting This clinical picture is characteristic but not diagnostic Blood calcium, phosphorus and phosphatase are normal, but roentgenograms are characteristic Age cannot be the only causative factor since most old persons are not so affected Treatment aims to replenish calcium and phosphorus in bones, it involves use of a diet rich in calcium and phosphorus, supplemented by calcium phosphate and vitamin D (e.g., tribasic calcium phosphate 1 drachm [4.0 gm]) and cod-liver oil (1 fluidrachm or 4 cc) three times a day before meals, also mild sedatives, heat, massage and support for the back (high backed corset) Despite prolonged treatment roentgenograms showed no recalcification but pain and progressive kyphotic deformity were relieved as shown by the fact that symptoms often returned when treatment was stopped

[Albright and his colleagues¹² have stated that many cases of postmenopausal senile osteoporosis are probably due to loss of estrin Estrogenic therapy will produce a positive calcium balance—Ed]

Postmortem studies on senile kyphosis indicate that the essential pathologic process is pressure necrosis of the anterior portion of the intervertebral disk (Saunders and Inman) The abnormal pressure on the anterior portion of the disk, leading to its necrosis, results from general loss of muscular tone in the aged and the failure of the senile inelastic disk to disperse adequately the compression forces applied to it The vertebral bodies do not become notably wedge shaped, since the anterior narrowing of disks is sufficient to account for the deformity

Backache and Sciatica from "Hypertrophied" Ligamenta Flava English reports thereon have been scarce, one appeared (Dickson and Twort)

Backache from Spinal Malignancy Seven patients were referred to Campbell¹³ presumably with "rheumatism" In each case the back or leg pains were due to carcinomatosis of bone Chief diagnostic criteria were the type of pain, anemia and (sometimes) the roentgenographic changes present Pain was severe, unrelieved by usual antirheumatic remedies, deep seated, gnawing and usually unrelated to movement, eventually it became more intense and continuous There was a hypochromic anemia or a myelogenous (leuko-erythroblastic) anemia—a moderately high color index and the presence of abnormal red and white cells, reflecting stimulation of bone marrow Erythrocyte counts were usually between 3,500,000 and

4,000,000, sometimes lower Roentgenographic changes were sometimes long delayed

[Of supplementary value to the above is the axiom of one of us, P S H In cases of rheumatism requiring narcotics, suspect malignancy"—Ed]

Backache from Spinal Actinomycosis A case was reported ²⁹²

BACKACHE AND SCIATICA FROM DISEASES OF INTERVERTEBRAL DISKS

An extensive review of the anatomy, physiology and pathology of intervertebral disks appeared (Saunders and Inman) The commonly recognized lesions of disks are senile fragmentation (without protrusion of disk material) and ruptured disks A third and little known condition also affects disks—lesions due to acute infections

Acute Infectious Lesions of Intervertebral Disks This lesion of the spinal column, involving chiefly the disks, with a more or less severe febrile onset, resulting probably from a primary or secondary infectious process was described by Ghormley, Bickel and Dickson It has erroneously been called "vertebral osteomyelitis," but involvement of vertebrae is negligible, hence the condition should be considered a separate entity It is a condition seen in some cases of "typhoid spine" and in spinal brucellosis Twenty cases were described Eventual thinning of the affected intervertebral space and later proliferation of new bone along vertebral margins occur Prognosis is excellent Treatment is by conservative orthopedic measures

Ruptured Intervertebral Disks From the great number of papers appearing thereon it might be assumed that this condition is very common, perhaps the commonest cause of backache and sciatica It was emphasized that such is not the case, the condition is fairly common but such cases still make up only a small percentage of cases of back pain and sciatica (Keegan and Finlayson) Many new American and one English series (Pennybacker) were reported

1 Cervical Region Cervical disks are rarely affected Stookey outlined symptoms of ruptured cervical disks Presenting symptoms may be pain or stiffness in neck, shoulder girdle, arm, forearm or hand depending on the segment affected There is gradual weakness and muscular hypotonia, atrophy and fibrillation—symptoms of nerve root pressure Roentgenograms (ordinary technic) may reveal a narrowed intervertebral space, but such a finding is so common without herniation of disk material that it is of no significance unless associated with positive neurologic findings Cervical myelograms cannot be made with lipiodol; for diagnosis a combined encephalogram and myelogram must be done with air Stookey's results with hemilaminectomy were satisfactory

2 Lumbar Region More than 90 per cent of protrusions of disk that cause symptoms occur in the last two disks, between fourth and fifth lumbar vertebrae and the lumbosacral disk ¹¹ Lumbar protrusions occurred in 96

per cent of 500 cases in which operations were performed by Love and Walsh. Among the many characteristic new cases reported, one case was unusual for several reasons. A lesion, thought to be a spinal cord tumor because of neurologic findings and complete spinal block revealed by spino-gram, proved at operation to be a calcified protruded disk between the tenth and eleventh thoracic vertebrae (Cohen)^{1,21}

A history of specific trauma was noted in 63 per cent of Johnson's 40 cases, in 58 per cent of the 500 cases of Love and Walsh. Special trauma was a feature of the case of a 14 year old girl reported by Gellman. It consisted of localized injury to intervertebral disks from several unsuccessful spinal taps. Successive roentgenograms revealed the resultant changes. Severe lumbar pain and hyperextension developed and later lumbar flexion and prominence of the spinous processes of the second and fourth lumbar vertebrae.

Statistics of the new series resembled those formerly reported. Sex incidence was 358 males to 142 females in one series,³⁷¹ 24 males to one female in another series.⁶⁰⁹ Sciatica was unilateral in 78 per cent, bilateral in 16 per cent, absent in 6 per cent of 500 cases studied.³⁷¹ Sciatica affected all the patients in one series⁶⁰⁹ but in one proved case "terrific lumbar backache" without sciatica was present (Baker and Soniat). Achilles reflexes were abnormal in 50, 60^{307, 371} and 70⁴¹⁸ per cent of cases. Lasègue's sign was positive in 84 per cent.³⁷¹ Motor changes affected 25³⁷¹ and 28³⁰⁷ per cent, sensory loss affected 21 per cent, sphincter loss, 4 per cent.³⁷¹ Symptoms were intermittent in 84 per cent of 500 cases,³⁷¹ in 96 per cent of 25 cases.⁶⁰⁹

"The one outstanding symptom in these cases is pain, not a mild sciatic pain, but a severe intractable disabling pain which may have long remissions. The one outstanding sign on physical examination is interference with straight leg raising" (Mixter and Barr). Spinal fluid proteins were less than 40 mg per 100 c c in 30 and 40 per cent of cases^{371, 371}, they were more than 40 mg per 100 c c in 65 per cent of cases.²⁹⁸ They are rarely more than 100 mg per 100 c c but they were enormously increased (to 3500 mg per 100 c c) in Bunt's case which simulated tumor of the cauda equina (complete spinal subarachnoid block, yellow spinal fluid).

Technic of myelography was described^{88, 89, 288, 475, 534}. Since in most cases back pain and sciatica clear up spontaneously or under conservative measures, myelograms should not be made "unless sciatica has been present months, not weeks" (Mixter and Barr). Robinson⁴⁷⁵ considered injections of lipiodol indicated only in cases in which spinal fluid protein is elevated, an adequate trial of orthopedic remedies has failed, some other definite explanation for the sciatica cannot be found, and sacro-iliac or lumbar fusion is contemplated. The use of lipiodol rather than air was preferred by many^{88, 288, 290, 418, 475}. Five cubic centimeters were used by some,^{88, 288} but Bell⁸⁸ considered 2 c c adequate and devoid of reactions. The technic involves a total diagnostic error of 11 per cent (Camp and Addington), but false negatives may occur (Mixter and Barr). The occasional reactions and dangers of lipiodol spinograms were noted^{288, 418, 475}.

Because of the irritating properties of lipiodol, myelography with air was preferred by some and considered reliable^{44, 104}. The accuracy of air myelography varies considerably in the hands of different workers, according to Hampton present methods

carry an error of 50 per cent, hence it is "unsatisfactory" (Johnson) Perfecting their clinical examination, Spurling and Grantham found it unnecessary to do either air or lipiodol myelograms in 50 per cent of their cases They regarded as "of extreme importance in the diagnosis of intraspinal lesions" the test of Naffziger and Jones (1935), performed by occluding both jugular veins until a sense of fullness in the head affects the patient and until his face is flushed "If the back pain or paresthesias in legs are reproduced by this maneuver, we consider the finding pathognomonic of intraspinal disease"

Treatment Before advising operation conservative measures should be tried rest in bed or use of plaster jacket or some other apparatus to hold the lumbar portion of the spinal column in flexion This may succeed,^{307, 413} but Mixter and Barr considered surgical removal more successful Instead of the classical laminectomy, surgeons are now using hemilaminectomy^{296, 307, 370, 371} or are even removing the disk material interlaminally, without removing any bone^{235, 309, 371} Fusion or bone grafting is rarely necessary even when laminectomy is done^{296, 307}, fusion was done in only 15 of 500 surgical cases (Love and Walsh)

Results of treatment continue to be satisfactory Patients were cured in from 47⁴¹³ to 83²⁹⁶ per cent of cases, "cured or markedly relieved" in 76³⁰⁷ to 85^{533, 534} per cent There were two deaths in 123 cases in one series,⁴¹³ two deaths in 500 cases in another series³⁷¹ (mortality 0.4 per cent) Recurrences were noted in 11,³⁷¹ 31,⁵³³ and 4 per cent²⁹⁶

RHEUMATOID (ANKYLOSING) SPONDYLITIS

The most important spinal joints, the apophyseal or posterior intervertebral joints, receive little attention from either roentgenologists, orthopedic surgeons or rheumatologists These apophyseal joints are true diarthrodial joints—they differ from the synchondroses formed by the disks and vertebral bodies almost as much as the hip joints differ from the pubic symphysis (Oppenheimer)⁴³³ Goldthwait noted that there are 44 true rib joints 12 costovertebral joints on each side where ribs join the vertebrae and 10 on each side of these where ribs touch the tips of the transverse processes These joints are seldom studied and are of great importance in ankylosing spondylitis

Etiology Lux proposed the thesis [on what appears to us to be inadequate evidence—Ed] that postural changes secondary to hereditary malformation of the epiphyseal ring of the vertebrae produce the most frequent forms of spondylarthritis No abnormality of sulfur metabolism was noted.²⁰⁰ Robinson¹⁷¹ showed that incidence of tuberculin sensitivity was 30 per cent higher in 45 cases of ankylosing spondylitis than in 90 rheumatic control cases (it was low in peripheral rheumatoid arthritis, a point of contrast with ankylosing spondylitis) No explanation was offered The antifibrinolytic content of plasma was practically always normal¹⁵¹

Clinical Data In two years at the Lahey Clinic, Hare saw 1,179 cases of arthritis (including 357 of rheumatoid arthritis), of the latter 21 (6 per

cent) were cases of rheumatoid (Marie-Stumpell) spondylitis, in only four of which peripheral joints were involved. He divided the disease into three phases. (1) prespondylitic phase, (2) phase of sacro-iliitis, (3) phase of poker back deformity. Roentgenographic findings in each phase were described. In all cases sedimentation rates were elevated. Edstrom posed the question, "Is spondylarthritis ankylopoietica an independent disease or a rheumatic syndrome?" After discussing each point of view he presented reports of seven cases, in six of which there was frank evidence of "chronic rheumatic infectious arthritis." In these six cases various mesenchymal organs were attacked by the rheumatic infection, and arthritis, peritendinitis, bursitis, endocarditis, pleuritis, iritis, subcutaneous nodules and changes in skin and nails developed. He concluded that spondylarthritis ankylopoietica is a rheumatic syndrome belonging to the group of "chronic rheumatic infectious arthritis" (i.e., rheumatoid arthritis). But Osgood regarded ankylosing spondylitis as an entity separate from rheumatoid arthritis.

[Evidence is accumulating that ankylosing spondylitis is only one expression of rheumatoid arthritis, but the point will doubtless be raised by proponents of the other viewpoint that many of the cases described by Edstrom were cases of rheumatoid arthritis with spinal involvement rather than true cases of ankylosing spondylitis. This criticism is perhaps justified in the case of the patient with subcutaneous nodules whose condition was diagnosed as "spondylarthritis ankylopoietica in the prespondylitic stage." The demonstration of subcutaneous nodules in unequivocal examples of ankylosing spondylitis would go far to settle the controversy—Ed.]

Roentgenograms Roentgenographic features were carefully reviewed by Forestier and Robert, also by Oppenheimer⁴⁸⁸ who has stressed the importance of the apophyseal joints for several years.

Oppenheimer described the appropriate technics for visualizing the joints—90 degree films in the cervical region, nearly 20 degrees in the thoracic region and 45 degrees in the lumbar region. Various developmental variations and anomalies were considered briefly and a detailed description of the changes seen in both rheumatoid and osteo-arthritis was presented. He concluded that both rheumatoid and osteo-arthritis of apophyseal joints are distinct from "so-called arthritis of the spine" which consists essentially of exostoses at edges of vertebral bodies. "The conception of arthritis, pertaining to lesions of diarthrodial joints, does not apply to the disc synchondroses either clinically or anatomically, the reactions at the edges of the vertebral bodies are *ostitic* but not *arthritic*. It is in the apophyseal joints that arthritis of the spine, a spondylarthritis, is localized."

[We agree—Ed.]

Treatment Roentgen therapy was recommended by Hare and Kimmel and by Hare. Results were "striking." In the first series of 21 cases relief of pain was complete in 13, partial in three, absent in five. Stiffness was relieved in 16 cases. In the second report on 35 patients treated, 80 per cent were relieved of pain. [These results are considerably better than those obtained by some, but compare well with the good results recently reported by Smyth, Freyberg and colleagues^{522, 523}—Ed.] Contrary to the opinion of some,^{6, 7} Tarsy considered chrysotherapy useful in rheumatoid spondylitis [data incom-

plete—Ed] But in such cases toxic hematuria from chrysotherapy seems more likely to develop than in rheumatoid arthritis, according to Sherwood results of gold in ankylosing spondylitis are "rarely good and the hematuria is so frequent that I now use gold rarely in spondylitis and only with a urinary analysis preceding each dose"

[Sherwood used very small doses of gold salts—Ed]

OSTEO-ARTHRITIC (HYPERTROPHIC) SPONDYLITIS

Few articles on spinal osteo-arthritis appeared. A careful anatomic and pathologic study of cervical intervertebral disks of 50 adult human cadavers was made by Horwitz. Exostoses were present in 70 per cent of instances and corresponded closely with the location of lesions in disks. Horwitz briefly discussed differential diagnosis of pains in neck, shoulder and upper extremity.

[Unfortunately in this as in many other such reports no correlation was made between clinical and pathologic findings—Ed]

Headache from arthritis of the cervical portion of the spinal column was described by Hartsock.

Ranking in frequency with ocular and migraine headaches, this type of headache invariably begins in the occiput and spreads upward and forward into the temporal regions as it becomes more severe. Of great diagnostic importance is the tenderness of the cervical muscle attachment to the skull. Headaches are periodical at first, lasting three to four days, coming on early in the morning and having a tendency toward long sieges of constant pain which may become chronic. A relation exists between the headache and exposure to draft, wetting of the hair or anything which causes tenseness of neck muscles. Crepitus frequently accompanies the headache and is audible when the head is turned from side to side. The headache occurs mostly in elderly (osteo-arthritic) persons, roentgen evidence of cervical osteo-arthritis is usually fairly obvious. A history of arthritic pains especially in the low back, knees and shoulders tends to confirm the osteo-arthritic genesis of these occipital headaches. Diagnosis is important, it relieves the patient's mind and obviates long and expensive search for another possible cause. Usual therapeutic measures were advised. Local injections of procaine for spinal osteo-arthritis gave results satisfactory to Lipkin.

GOUT AND GOUTY ARTHRITIS

Physicians are fortunately becoming more "gout-conscious" ^{131, 217, 258, 259, 754, 572}. Those interested in the history of gout will enjoy a new printing of Sydenham's "Treatment of gout and dropsy" and Hormell's fine note on the history of rheumatism and gout.

Incidence Gouty arthritis made up 2 per cent of all cases seen in the Rackham Arthritis Research Unit,²⁰² about 5 per cent of arthritic cases seen at the Cleveland Clinic,⁷²⁴ and about 4 per cent of all cases at the Red Cross Rheumatism Clinic, London.⁵⁰⁸

Factors Governing Incidence 1 *Heredity* Contrary to British experience, few American victims of gout can trace the disease in their an-

cestois But the hereditary factor is an important one, in some cases at least, as shown by recent studies demonstrating notable symptomless hyperuricemia in a significant percentage of male relatives of gouty patients^{521, 504}

Twenty-seven gouty patients of Talbott had 136 blood relatives, none of whom had symptoms of gout. Concentrations of serum uric acid of 75 per cent of these relatives were normal (less than 6 mg, average 4.6 mg), of the rest elevated (6.1 to 10.8 mg, average 7.3), 83 per cent of the relatives who had hyperuricemia were males, subsequently three had acute gouty arthritis. Smyth and Freyberg studied 29 immediate relatives of two gouty persons. In one family the father and three sons had proved gout, the fourth sibling (a daughter) had no attacks but had a high normal value for serum uric acid. In the second family the father had gout, two sons had symptomless hyperuricemia (7.9 and 8.4 mg per cent), another son had a high normal (5.6 mg per cent) and a daughter a normal, value for serum urates. Thus of the eight males in these two families, five had active gout, two had symptomless hyperuricemia [larval gout?—Ed], and one had a high normal concentration of serum uric acid, of the four females none had active gout, two may or may not have had larval gout (high normal values for uric acid) and two had average normal urate concentrations.

[These interesting studies confirm that of Jacobsen⁹]

2 Sex The studies just mentioned indicate again that females, even in gouty families, are much less liable than males to have active gout. Of the new cases of gout only 3.5 to 7.4 per cent were in females (three of 62 cases³²⁴, three of 85¹⁸¹, two of 27⁵⁰⁴). Claiborne reported an interesting case of a 17 year old girl with prelophaceous gout of three years' duration.

3 Age The average age of Kinell and Haden's patients was 50 years, their symptoms had lasted an average of seven years, in 60 per cent their first attacks occurred between the ages of 33 and 50 years. Coomb's patients were from six to 72 years old at the time of initial attacks.

[Cases of provable gout in young children are very rare—Ed]

Clinical Data Patients with gout, currently reported, exhibited the classical features of gout, despite which a correct diagnosis had often been long deferred. The first joint affected in the Cleveland cases³²⁴ was the "first toe joint" in 53 per cent, a "foot" in 17 per cent, thus in 47 per cent the first toe was not affected and in 30 per cent the original attacks did not affect any part of the foot.

1 Provocatives Among susceptible persons liver extract may provoke acute gouty arthritis. Two such cases were reported. A man with tophaceous gout and congenital hemolytic icterus developed acute gouty arthritis "immediately following a liver injection"¹⁵⁰. A man with pernicious anemia was given, intramuscularly, liver extract on six successive days, a day or two later acute gouty arthritis developed⁴⁸⁴. These attacks were thought to be related to increases of endogenous uric acid accompanying "reticulocyte crises" these increases result from the destruction of erythrocytes in hemolytic jaundice and the augmented nuclear material liberated during blood regeneration when normoblasts lose their nuclei to become normocytes. [One of us, W. B., has been giving every two or three weeks injections of liver extract to two patients with gout and pernicious anemia, the injections do not seem to provoke gouty arthritis—Ed]. Severe hemorrhages and transfusions have been cited as provocatives. A man with severe anemia as a result of melena for three days, received a transfusion, a few days later acute gouty arthritis developed⁴⁸⁴. Surgical operations may provoke gout. A woman with tophaceous gout and hemolytic icterus developed acute gouty arthritis five days after splenectomy, but her son, with the same complaints, endured splenectomy

without acute postoperative gout¹⁵⁶ A boy with "erythronoclastic anemia" had an acute attack of gouty arthritis three days after splenectomy³¹⁰

2 Tophi In one series of cases tophi were present in 23 per cent³²⁴ Tophi are uncommon in women and children Tophaceous gout was seen in three women^{434, 564} and in two boys 14 years old with blood dyscrasias^{340, 434} In one case tophi developed before the onset of joint symptoms (Kinell and Haden) Authentic reports of endocardial or valvular tophi are extremely rare, of much interest, therefore, is the case of Bunim and McEwen of a urate tophus of the mitral valve crystals were removed from the concretion and microscopically identified as urates

[Unfortunately the gross specimen was fixed in a solution which dissolved urates, hence in the sections, only circumscribed masses of amorphous eosinophilic material were seen To prevent dissolution of urates suspected tissues should be fixed, not in the usual formalin-containing fixatives, but in absolute alcohol (de Galantha method, 1935) Another intracardiac tophus was seen by one of us (Hench and Darnall, 1933)—Ed]

3 Renal Stones In one series 11 per cent of the patients had renal colic (Kinell and Haden), in another 30 per cent (Coombs et al)¹³²

4 Unusual Clinical Features The association of gout and blood dyscrasias is greater than possible by mere coincidence Deitrick noted three cases of congenital hemolytic icterus and gout, in one case no gouty attacks occurred for at least seven years after splenectomy A boy with tophaceous gout (at the age of 14 years) and "chronic erythronoclastic anemia" was studied in great detail by Lambie The boy was frequently jaundiced but none of his relatives had hemolytic anemia

[We cannot review adequately this excellent, informative case report Students of gout are urged to read the original—Ed]

Irregular Gout Three cases of "ocular gout"³³¹ and one of "gout of the auditory apparatus" simulating Ménière's disease¹⁴⁸ were reported [We cannot accept the interpretations given Two of the three patients with "ocular gout" were females, all three had ill defined "rheumatic pains" and slight hyperuricemia, none had classical attacks or tophi The patient with Ménière's disease had had two attacks of "gouty arthritis" but no attack associated with the vertigo No tophi were present, no studies of concentration of uric acid were made, no colchicine test was done—Ed]

Laboratory Data 1 Relation of Blood Uric Acid to Gout There is no "uric acid" in blood; the substance is in the form of sodium biurate, hence we should speak of blood urates^{131, 199} In 82 per cent of the cases of Kinell and Haden a blood level of 3 mg per cent or more was found (the Morris-MacLeod technic was used by which 2.5 mg per cent is considered the upper limit of normal) But patients may have proved tophaceous gout with normal blood urates²²⁴ There was a general but no absolute correlation between the degree of hyperuricemia and the stage of the disease or attacks in the cases of Kinell and Haden A similar conclusion was made by Brochner-Mortensen who published a 40 page monograph on the uric acid content in blood and urine in health and disease

2 *Sedimentation Rate* Rates were elevated in 85 per cent of 62 cases and varied with the clinical activity of the disease³²¹

3 *Blood Counts* "The ruddy complexion of the gouty patient" is due to "plethora" of the Cleveland cases erythrocyte counts were more than 4,800,000 in 50 per cent, more than 5,000,000 in 24 per cent³²⁴

4 *Roentgenograms* "Positive roentgen evidence of gout" was found in only 31 per cent of the Cleveland cases. Such evidence was seen in one case two months after onset of symptoms, but was still absent in certain cases in which symptoms had been present for 25 to 30 years³²¹

5 *Renal Function* This was impaired to some degree in 18 of 22 cases studied by Coombs and colleagues

[These were not run of the mill cases of gout, but a select group of late cases as shown by the fact that of the 22 patients 17 had subcutaneous tophi, 12 had osseous tophi and seven had renal urate stones. Hence the conclusions drawn from this study are applicable only to late progressive gout—Ed]

Etiology Gout is a "disturbance of the solubility of uric salts which in extreme cases involves their crystallization in tissues", normally "the proteins of blood protect the sodium biurate against agglomeration which would take place in the same concentration in a physiological solution. In gout the protective colloidal property in the tissues is destroyed". Such was the theory of Sedlacek who isolated a "substance" from urine considered by him to be the cause of gout. According to Terray, "Everyone knows that the acute attack is caused by the precipitation into the joint of uric acid crystals"

[As a matter of fact nobody knows this for certain, and many authorities have abandoned this concept of the attacks—Ed]

Treatment There was no dispute as to the value of orthodox treatment for acute attacks (Bauer and Short, Hench). "No benefit has been derived from colchicine except in patients with gout and no patient with proved gout has failed to be greatly benefited by it"²⁰² "We have never seen colchicine fail to give relief"⁸¹ Enough to give relief should be prescribed even if that amount produces diarrhea. There was no agreement, however, as to what constitutes a "diarrhea-dose" of colchicine. Some said 8 to 16 doses,⁸¹ others²⁰² said 14 to 25 tablets, according to others¹⁸¹ 8 to 19 (in each report the dose was grain $\frac{1}{120}$ every one to two hours). [In our experience it is about 6 to 18 (in one case, 24) $\frac{1}{100}$ grain tablets given one every one to two hours—Ed]. The value of "interval-treatment" was in dispute. Several physicians^{110, 258, 279, 388, 572} considered it definitely useful but workers^{81, 181} at the Massachusetts General Hospital again disputed this idea. They avoid cinchophen and rely on "a sensible diet" which merely excludes the concentrated purines. Sedlacek treated gouty patients with parenteral injections of his "substance", nothing daunted, he claimed "all kinds of arthritis show improvement or healing on parenteral application of the substance"

[Difficult to believe!—Ed]

Studies on Colchicine Newer studies on the effect of colchicine on the growth of normal and malignant tissue cells have not explained its action in gout. The

toxicity of colchicine may be related to hepatic function Colchicine given to rats with acute hepatic damage or within five days of partial hepatectomy caused serious, often fatal, reactions Similar doses were well tolerated when livers had had time to regenerate Colchicine may or may not be detoxified in the liver but the drug should, perhaps, "be used with caution in treating patients with disease of the liver" (Scherfley and Higgins)

Cinchophen Toxicity Four cases of cinchophen toxicity were reported, again *none were in gouty patients* An osteo-arthritic patient took cinchophen, grains 15, daily for six days, urticaria and moderately severe (non-fatal) toxic hepatitis developed A man with pains in chest and shoulder took cinchophen (amount unknown) fatal toxic hepatitis ensued (Berry) A mother and her son took "guaiacin" capsules, Massengill (guaiacol ester of phenyl-cinchoninic acid) for colds The mother developed nonfatal toxic hepatitis and a duodenal ulcer "produced possibly by the cinchophen" [If so, it is the first human case on record—Ed] The son died of acute yellow atrophy (Mac Bryde)

[We believe that cinchophen should never be given for any type of arthritis except gout, and then only when the gout cannot be controlled adequately by other measures Some of us do not use it even then—Ed]

Further studies on cinchophen ulcers in dogs and in chicks appeared ¹⁵², ⁴²⁵, ⁵⁶⁷, ¹⁰⁷ The excretion of cinchophen in bile was studied ⁶³

Uric Acid Problem Further studies were made with the uricase method for determining the "true uric acid" content of blood ⁷, ⁴⁰¹ Bjørchner-Møntensen's excellent monograph cannot be reviewed adequately here To him it seemed probable that between 90 and 95 per cent of the uric acid which is filtered through glomeruli is reabsorbed by tubules High fat diets seemed to increase the amount of resorbed urates to 99 per cent of that filtered [In other words high fat diets do not prevent glomerular excretion but enhance tubular resorption of urates But the end result is the same, the urates do not pass into the bladder but reenter circulating blood—Ed] Cinchophen and salyrgan depress tubular reabsorption of urates, hence they increase urate clearance of normal and gouty persons unless advanced renal insufficiency is present, according to Coombs and his colleagues These workers believe that cinchophen damages normally functioning cells of the tubules and prevents reabsorption of urates just as salyrgan damages tubular cells and prevents reabsorption of urates, sodium and chloride [This is theory, not fact—Ed] Colchicine appears to have no effect on the renal excretion of urates

PSORIATIC ARTHRITIS

No reference to psoriatic arthritis was made except a statement by Bauckus and Kwak "There is universal belief that arthritis may be a part of the psoriatic syndrome"

[Whether psoriatic arthritis is a separate entity or represents rheumatoid arthritis with coincidental psoriasis remains in dispute Certain features presumably characterize psoriatic arthritis these are asymmetrical peripheral arthritis with frequent involvement of terminal phalangeal joints of fingers and toes, psoriatic changes in adjacent nails, exacerbations and remissions of the joint manifestations "reasonably synchronous" with those in skin—Ed]

Incidence No new data on the incidence of psoriatic arthritis appeared Ap-

proximately 200 cases have been reported.⁷ Psoriasis constitutes about 4 per cent of all skin affections in America.⁴¹³

Etiology Various theories were discussed^{356, 379} Lerner found that 42 per cent of 172 patients with psoriasis gave a history of the disease in their immediate families

Treatment The treatment of psoriasis remains as controversial as its etiology. The value of local therapeutic agents was discussed^{80, 843} Vitamin D preparations were considered safe but unreliable by Clarke,¹¹¹ useless and dangerous by Madden. The latter obtained best results by using a low fat diet, vitamin B₁ (1,000 international units daily) and an exfoliating ointment. Ascorbic acid, estrogenic substance, anterior pituitary extract, adrenal cortical extract, sulfanilamide, and bismuth salicylate were considered of no value but eight of 35 patients treated with liver extract and dilute hydrochloric acid improved.⁷⁷⁹

HEMOPHILIC ARTHRITIS

Clinical, pathologic and roentgenographic aspects of hemophilic arthritis were reviewed (Caffey and Schlesinger). Although articular changes develop prior to adolescence in 89 per cent of cases of hemophilia and hemiarthrosis (Thomas, 1936), little attention has been given to accelerated epiphyseal maturation associated with juvenile hemophilic arthritis.

Caffey and Schlesinger studied roentgenographically the joints of five children with recurrent hemophilic hemiarthrosis. Accelerated maturation of the epiphyses was present at the knee and elbow in one case, at the elbow in a second, in a third case hypertrophy and fragmentation of the radial capitulum were present, a fourth case showed marked increase in size of the epiphyses of the femur and tibia, and enlargement of patella, a fifth case exhibited coxa plana of the hip joint resembling Perthes' disease. Measurements of the effect of chronic hemiarthrosis on diaphyseal growth were not made, but overgrowth of an extremity following hemorrhage into a knee has been reported. Accelerated epiphyseal maturation was explained on the basis of chronic irritation and chronic hyperemia induced by repeated hemorrhage, but attempts to accelerate epiphyseal development experimentally by injecting heparinized blood into joints of growing rabbits were unsuccessful. Newer agents to lower coagulation time of patients with hemophilia were described.^{352, 397, 437}

ALLERGIC ARTHRITIS

"The arthritis of serum sickness is the only type of arthritis that can be classified as anaphylactic or allergic in nature" (Bauer and Short). The absence of a single article under the title "allergic arthritis" in the American and English literature of 1940 rings a note of encouragement. The term, like "metabolic arthritis," is falling into disuse.

METABOLIC ARTHRITIS

No articles under this title appeared.

ENDOCRINE ARTHRITIS

Thyroid Dysfunction and Chronic Rheumatism Thyroid dysfunction has been blamed as a causative factor in arthritis.¹⁶⁰ Hoskins maintained

that a "thyroid deficiency type" of osteo-arthritis exists, and that the subsidence of joint symptoms is "often miraculous" when thyroid extract is administered

[The author seemed overenthusiastic about several forms of therapy. Muscle and joint pains occasionally accompany the thyrotoxic state and are frequent complaints in myxedema, but proof is still lacking that any thyroid abnormality can cause arthritis—Ed]

Menopausal Rheumatism The literature of 1940 contained no new data concerning this controversial subject^{166, 216} which was thoroughly discussed in a previous Review⁶

[Writers do not agree as to what constitutes the clinical or pathologic picture of so-called menopausal rheumatism. The rôle played by the climacteric as a predisposing, contributing or causative factor in any of several forms of arthritis also remains in debate. Most American and Italian⁴⁶⁴ rheumatologists are reluctant to accept the term "menopausal arthritis"—Ed]

Joints and Parathyroid Glands No known type of arthritis is caused by disease of the parathyroid glands⁴⁶⁴. Skeletal and muscular pains especially in back, legs and arms, subjective stiffness, muscular hypotonicity, weakness and fatigability are often present in cases of hyperparathyroidism⁴⁶⁴. Joint pains occasionally may predominate early in the disease but are not to be confused with arthritis⁶⁰. An interesting, and if confirmed, important new concept of parathyroid function was presented by Helfet. He considered that an accumulation of phosphate in the blood stimulates an increased secretion of parathyroid hormone. He reduced the levels of serum calcium and plasma phosphorus by the oral administration of aluminum acetate which diminishes the absorption of phosphates from intestines. The clinical and roentgenographic improvement with such therapy in cases of generalized osteitis fibrosa cystica due to "secondary hyperparathyroidism" was impressive.

[We have commented elsewhere herein on this report—Ed]

MISCELLANEOUS TYPES OF JOINT DISEASE

A "New, Oft-Recurring Disease of Joints" An oft-recurring disease of joints apparently producing no residues was described by Hench²⁵⁷

Outstanding features were multiple afebrile attacks of acute arthritis and peri-arthritis, sometimes also para-arthritis, with pain, swelling, redness and disability, generally of only one, but sometime of more than one, small or large joint of adults of either sex. Attacks appear suddenly, develop rapidly, generally last only a few hours or days and then disappear completely, only to recur at short or long irregularly spaced intervals. Despite the transitory presence of an acute or subacute inflammatory reaction in joint tissues and a fibrinopurulent exudate in articular cavity in some cases, little or no significant functional, pathologic or roentgenographic residues occurred even after years of disease and scores or even hundreds of attacks. Thirty-four cases were summarized.

[A detailed report will soon appear—Ed]

Pharmacutic Arthralgia Pains in joints and bones occurred in a few cases in which arsenic, iodobismutol or maphaisen was being given. Such pains may be prevented by liver therapy, according to MacKee and Astrachan.

"Synovitis" An unusual form of transitory synovitis of the hip joint of children was described (Rauch).

Diagnosis was made by exclusion by ruling out all other forms of hip disease, and by observing the patient for several years to see that the disease was not only benign but transitory, this is a form of "observation hip." A list of 40 conditions resembling transitory synovitis was given. In the 37 cases described, the synovitis lasted for from seven to 60 days, an average period of 32 days was needed for recovery. Conservative treatment was advocated, especially rest in bed. Follow-up physical and roentgen examinations were made at the end of one, six, and 12 months and yearly thereafter for three years.

Tumors of Synovia and Joint Tissue The general characteristics, classification and differential diagnosis were reviewed by McCurdy.

1 *Synovioma* Clinical and pathologic features of synovial tumors were presented and a synovial tumor of the foot was described by Black. It was presumably benign and of bursal origin. The relative rarity of benign tumors of this type was emphasized. The roentgenographic recognition of synovioma was discussed by Lewis³⁶⁸ an unusual and striking roentgenographic appearance was observed in four cases.

"Near a joint, and sometimes involving a joint, is seen a rounded, sometimes rather lobulated, sharply defined soft tissue tumor mass. No differential diagnosis may be made on such a mass in itself, but when in the mass is found a scattered and irregular deposit of amorphous lime, we have learned that a provisional diagnosis of synovioma is justified." No other condition simulates this. Calcifications in angiomas are orderly and are in the characteristic form of phleboliths. Exostoses and osteochondromas are more extensively calcified and have the orderly pattern of bone throughout, except in their cartilaginous caps where the deposit of lime may be irregular.

2 *Synovial Granuloma* Spontaneous hemarthrosis attributable to synovial granuloma was reported (Stack).

3 *Chondioma* Fifty-six loose bodies (chondromatoses) were removed from a shoulder joint.⁴⁰⁷

Pulmonary Osteo-Arthropathy Pulmonary osteo-arthropathy may be the first symptom of an intrathoracic tumor. In two of seven cases reported by Van Hazel symptoms disappeared abruptly following removal of the tumors. In some cases the condition simulated arthritis.

[In discussion it was noted that no single explanation was adequate for the occurrence of club fingers in all the different conditions in which it is found. The condition has never been reproduced experimentally.—Ed.]

Cutis Elastica Ehlers-Danlos Syndrome Three typical cases were reported, showing hyperelasticity of skin, over-extensibility of joints and fragility of skin and blood vessels.^{117, 421, 511}

Osteochondritis Dissecans Cases involving unusual locations were reported: two typical cases of a hip,³²⁵ one involved a metatarsal head,⁹⁷ and three cases involving respectively the elbow, ankle and metatarsal phalangeal joints.⁹⁵ The etiology, pathology, clinical picture, roentgenologic findings, diagnosis and treatment were reviewed.³⁸⁰

Changes in Joints from Interrupted Articular Circulation 1 In Caisson Disease An interesting paper dealing with the skeletal manifestations of caisson disease was contributed by Coley and Moore

Attention was called to caisson disease as a possible cause of bone and joint pains which may be discovered later to be due to "silent" areas of aseptic necrosis. Long bones are favored sites for symptoms; 70 per cent of symptoms occur in lower extremities, chiefly knees. German authors described 11 cases, in all of which lesions involving a large joint were present: a hip was affected 12 times, a shoulder once. In all cases, except two the arthritis was monoarticular. The pathologic reaction results from nutritional interference either from direct embolism in a main nutrient vessel or from pressure on the vessel wall by bubbles or by both of these means. A deforming osteo-arthritis ensues as a result of absorption, collapse, and formation of new bone in or near the epiphysis. Caisson disease may be recognized in roentgenograms by multiple distribution of infarcts in the medullary bone, changes in cortex are rare. The process may be explained on the basis of vascular insufficiency and nutritional disturbance. Two cases were reported.

Another case of caisson disease was reported (Gordon and Heacock). A tunnel worker fractured both tibiae. He was removed to a hospital too hastily to permit adequate decompression. Roentgenograms revealed gas in synovial sacs of both knees. Later the gas was absorbed and there was no permanent articular injury.

2 From Injuries Interruption of circulation to joints may result from injury, subsequent changes simulate those which may occur in caisson disease. Phemister has amplified studies noted in our last Review. Fractures bordering on joints in certain locations (especially neck of femur, carpal navicular bone and condyles of humerus) may result in extensive severance of connections and aseptic necrosis of the bone of the articular fragment. There is predisposition to nonunion by displacement and by interference with callus formation from the articular fragment. Articular cartilage undergoes nutritional disturbances which contribute to the later development of "arthritis deformans" [i.e., osteoarthritis] and osteocartilaginous loose bodies. If the fracture unites but later functional stress and strain are too great, the bone collapses and the joint becomes deformed.

Pelvic Arthropathy of Pregnancy Young⁶⁰¹ amplified his previous report⁷ on this condition which affected 0.75 per cent of 4512 pregnant women. The degrees of relaxation of pelvic (sacro-iliac and pubic) joints which normally occur during pregnancy are meager and symptomless but in the cases studied they were excessive and produced pain and tenderness in the pubic and sacro-iliac regions which appeared usually about the sixth or seventh month of pregnancy, sometimes earlier. In most cases of such pelvic arthropathy sacro-iliac joints were affected without pubic abnormality. Treatment for mild cases was use of corset and rest, for severe cases com-

plete rest in bed, for those with persistent sacro-iliac backache forcible manipulation (Bankart method, 1932) was best and gave complete relief to 68 per cent of 25 patients so treated

DISEASES OF BURSAE

General Comment The general problem of bursitis was discussed by Stimson. Etiology is usually trauma, infection or "toxins". Therapeutic aspiration, stab drainage and incision were condemned, injection of sclerosing fluids was discouraged. Conservative treatment with rubber sponge pressure dressings was recommended. Complete excision was performed when conservative treatment failed. In cases of olecranon and prepatellar bursitis and of inflammation in adventitious bursae Sarma obtained good results by injecting quinine urethane and a 5 per cent solution of sodium morrhuate. Excision was performed for recurrences which were rare.

Special Types of Bursitis Historical aspects of "miner's elbow" were presented, with old (1842) descriptions of olecranon bursitis.⁴⁷⁸ Salsbury discussed the anatomy of the ulnar bursa, in most cases a normal communication exists between the bursa and the digital sheath of the fifth finger.

Hyoid bursitis was described as a new disease entity. Nelson observed 31 cases, mostly in women, etiology was probably infection of nose, throat or teeth. Symptoms included soreness of throat on swallowing or talking, and tenderness at the tubercle of the greater cornua of the hyoid bone. Salicylates gave relief.

Cases of tuberculous bursitis about the femoral trochanter were reported.⁵⁸⁰ Stimson discussed olecranon, radiohumeral, iliopectineal, ischial, gluteal, prepatellar and infrapatellar bursitis and problems of bursae of the hamstrings, ankle and foot.

DISEASES ABOUT THE SHOULDER JOINT THE PAINFUL SHOULDER

General Comment Common lesions producing "painful shoulder" were discussed.^{207, 305} Many of them are due, not to "wear and tear" but to "tear and wear," according to Bosworth who noted, at operation, lesions in the following incidence: tendon lesions 24 cases, bursal lesion three cases, exostosis two cases. The tendon lesions included laceration or avulsion of one or more short rotator tendons in 17 cases, complete avulsion of the short rotator cuff in four, calcification or ossification of supraspinatus tendon in two, separation of the supraspinatus and infraspinatus muscles and tendons in one case. Diagrams of all these lesions were published.⁶⁹ According to others the commonest cause of painful shoulders is bursitis.^{207, 440} In the 104 cases of Patterson and Patterson the following diagnoses were made: bursitis in 70 cases (with calcification in bursa or tendon in 55, without calcification in 15 cases), periarticular inflammation in 15, sprain or subluxation in eight, arthritis in six, rupture of supraspinatus tendon in three, congenital deformity in two. In 53 per cent of Wilson's cases lesions of the sub-

acromial bursa were responsible for symptoms, in others they were due to lesions of bones, shoulder or acromioclavicular joint, muscles, tendons and vessels. The chief designation used by Solomon was "periarthrits," the result of adhesions and cicatricial formation subsequent to subdeltoid or subacromial bursitis. Myocardial infarction was the cause of pain in the shoulder in 17 of 133 cases (Einstene and Kinell).

[Obviously many different lesions are responsible for pains in the shoulder. It would appear that physicians tend to lump their cases of "painful shoulders" under a favorite diagnosis, whereas surgeons, having explored the lesions, make more varied and specific diagnoses. But from surgical reports the relative incidence of these lesions cannot be determined finally because the patients operated on are likely to have the more serious lesions, ruptures, avulsions, etc.—Ed.]

Subdeltoid or Subacromial Bursitis Current writers shared the opinions of previous workers^{6,7} that inflammation of these bursa rarely occurs primarily but almost always as a result of lesions in contiguous tissues, the floor of the bursa, the supraspinatus tendon or the musculotendinous cuff made up of the tendons of the supraspinatus and infraspinatus and teres minor muscles. In these tissues attritional changes often occur, with or without deposition of calcium salts, in the middle-aged. The pathogenesis of the lesions was again described^{74, 873, 390, 100, 440, 520, 591, 604}. Many calcified bursae are symptomless, in three cases such symptomless bursae were blamed for pains later proved to be due to pulmonary apical neoplasms⁴²². Calcifying tendinitis about the shoulder has its counterpart in lesions about other joints such as elbows and knees⁷¹.

Treatment For cases of "acute bursitis" or "acute calcareous tendinitis" most physicians recommended the injection of procaine hydrochloride into the affected tissues, aspiration of exudate or calcium containing material, and multiple needling of the bursa under local or general anesthesia^{805, 317, 302, 375, 400, 110, 604}. It is the multiple needling, relieving tension in inflamed parts and not the anesthetic agent or the aspiration which is responsible for relief⁵⁸⁹. Most physicians used the "two needle technic". Only one shoulder should be treated at a time, the procedure is best done in hospital⁴⁴⁰. Injection and needling are not so useful in chronic cases. Others^{20, 591} preferred removal of acutely inflamed bursal tissue and evacuation of calcium material surgically rather than by "blind needling".

For less acute cases or for those patients who will not permit needling and irrigation, rest in abduction, and physical therapy (diathermy) were advised^{317, 375, 513, 601}. Wilson considered diathermy useful in some cases, useless in others. Solomon and Weeks regarded diathermy as contraindicated in acute cases. Heat merely increases congestion and tension, cold applications for the first 48 hours were preferred. In chronic cases especially of contractures due to capsular adhesions, relief is often provided by conservative measures: physical therapy and "traction-suspension"^{400, 601}. Roentgen therapy was considered useful by some^{307, 59-} in 16 of 22 cases of bursitis, with or without calcification in which this treatment was used, com-

plete relief was obtained ³⁰² [Two of us, R H F and J A K, have seldom found roentgen therapy valuable in such cases—Ed] For chronic cases in which motion is limited by "matte adhesions" manipulation under anesthesia was considered dangerous by some,¹⁰⁰ valuable by others^{317, 318, 526} who described their technic and supplemented manipulation by traction in abduction and the use of an exerciser For ruptured tendons surgical repair is required⁴⁰⁰, a new technic was described⁵⁰

DISEASES OF MUSCLES AND FIBROUS TISSUE

Diseases of Muscles Caused by Trauma 1 Myositis Ossificans Twenty-five cases were reported among athletes (Thorndike) The disease begins as an inflammatory process with tumor, dolor and calor Treatment recommended was rest, the immediate use of cold, and a compression bandage to control hemorrhage, later the use of heat to absorb the hematoma Massage or exercises should be avoided In 36 per cent the ossification was entirely absorbed Operation is only required (12 to 24 months after injury) if joint motion is impaired [The origin of the term "charley-horse" was given by Thorndike] Shipley described two cases of ossifying hematoma erroneously considered sarcoma

Fibrositis A common cause of disability among soldiers of the British Expeditionary Force (1940) was fibrositis (Copeman) The clinical, laboratory and supposed pathologic features of fibrositis were described in the usual manner^{138, 230, 311} Fibrositis was again separated into primary and secondary types Slocumb³¹⁶ outlined the clinical and laboratory differentiation between primary periarthritic fibrositis and early rheumatoid arthritis The ameliorating effect of jaundice on primary fibrositis was discussed further²⁶⁶ Fibrositis of ligaments and muscles of back may simulate visceral diseases, such as chronic cholecystitis, appendicitis, duodenal ulcer, etc, according to Harman and Young But many cases of so-called fibrositis are really cases of "psychogenic rheumatism" (McGregor)

[It is unfortunate that such a common, or commonly discussed, condition as fibrositis has not been the subject of more original work As we have stated before, there is probably more copy-work in the discussions on fibrositis than in those of any other "rheumatic disease" One current writer³¹¹ who appended no references to his paper, borrowed with little change large sections from the writings of others outlined in recent Reviews—Ed]

1 Etiology, Pathology No new data were presented

2 Treatment of Primary Fibrositis This remains as outlined in recent Reviews Recommended were removal of infected foci, correction of postural defects, avoidance of mental and physical exhaustion, and various forms of physical therapy "rest, warmth, purgation, sweating and massage"^{138, 311, 577} Massage over tender spots "to break up the fibrous nodules" was again recommended as the most important single remedy^{138, 230, 311} If this does not give relief, the painful spots or tender fibrous

nodules should be needled with 1 to 5 c c of 0.5 per cent procaine hydrochloride^{183, 184} or with 5 to 30 c c sterile 2 per cent procaine^{88, 811}. The use of histamine by iontophoresis or by injections was again recommended^{183, 811}. Of 30 fibrositic patients given histamine by cataphoresis by Kling 61 per cent were "cured," 39 per cent were benefited. Only two of 13 fibrositic patients given injections of bee venom were improved⁵⁴⁰. In cases of old fibrositis of back muscles manipulation was recommended^{32, 183}. To prevent exacerbations of fibrositis patients should try to avoid respiratory infections, chilling, dampness and fatigue^{183, 811}.

Dermatomyositis Primary Polymyositis Chief anatomic features of this rare disease are nonsuppurative inflammation and degeneration of many muscles or even of the entire skeletal musculature. Articular symptoms may also occur. Among 40 cases of dermatomyositis O'Leary and Waisman noted "arthritis" (not defined) in two, transient arthralgia in four. Swollen joints and flexion contractures were present in two of the five cases of Kinney and Maher. Study of earliest muscle lesions indicated that the primary reaction may be manifested by the sarcoplasm rather than by interstitial cellular infiltration⁴⁸¹.

Infection or other disease commonly preceded the onset of the disease in the cases of O'Leary and Waisman. Present were varied skin lesions, muscle pain and weakness, vasomotor abnormalities, joint contractures, edema, increased creatinuria and low grade fever. In severe cases death may result, usually from respiratory or cardiac involvement. When the disease is less acute, it may subside, and partial recovery may occur, usually, however, with sequelae. Of 38 patients on whom followup studies were made, 19 died within four months to six years. Other cases were reported^{104, 198, 227, 210, 350}. English authors^{104, 198, 350} after pathologic study of skin and muscles stated their belief that the underlying pathology in dermatomyositis is identical to that of generalized scleroderma; they merely present different aspects of the same disease. Dermatomyositis must be distinguished from generalized scleroderma, trichinosis, disseminated lupus erythematosus, arthritis, Addison's disease, and periarteritis nodosa. Keil discussed the differentiation of dermatomyositis from disseminated lupus.

Treatment is empiric and difficult to evaluate. Fever therapy combined with oxygen inhalation was considered "decidedly of value" in some cases⁴⁴¹. One hundred grams of wheat germ oil daily were said to be beneficial⁴¹¹.

Trichinosis A rapidly fatal case of trichinosis with myocardial involvement was mistaken for rheumatic fever⁵⁶⁰. High frequency radiation (+75 mcgacycles) markedly retards the development of larvae of *Trichinella spiralis*²⁷⁴.

Psychoneurotic Rheumatism Several cases of psychoneurotic (muscular) rheumatism were described by McGregor who explained the pains occurring in these patients as a symbol of the individual's cramped existence (mental strain and emotional disturbance). "Rheumatism without structural change is nearly always psychogenic." Psychotherapy was often successful.

[In most of the cases described by McGiegor as well as those discussed by Halliday a diagnosis of "fibrositis" had been made previously. Students of rheumatism would do well to study these case reports so that the diagnosis of fibrositis be not so indiscriminately made.—Ed.]

Miscellaneous Myopathies Advances in the treatment of the myopathies were discussed (Milhorat). Myasthenia gravis is said to be benefited by prostigmine, ephedrine, guanidine, and amino-acetic acid. Progressive muscular dystrophy occurring in later life may be helped by amino-acetic acid. Quinine is effective in myotonia congenita and in the muscle rigidity of paralysis agitans. Potassium chloride is a specific for familial periodic paralysis.

MISCELLANEOUS CONDITIONS

Periarteritis Nodosa Clinical features in the 395 reported cases were summarized by Boyd. 280 patients were males, 108 females, the sex of seven was not stated. Rheumatic fever often antedated the periarteritis which suggests, with other data, a connection between the two diseases. There was a tendency for articular and neuromyositic symptoms to appear early, often as the first or second symptom to appear. Exclusive of "arthralgias," neuromuscular symptoms affected 129 of the 395 patients. Large joints such as knees, elbows, wrists or "all joints" may be involved. The combination of arthritis, cutaneous lesions and gangrene has occurred. Articular symptoms generally fade into the background as the syndrome progresses. Of 29 new cases reported in 1940, muscle pains were present in all, joint pains and disability in 13, articular swelling in only four. For diagnosis muscle biopsy should be done, but a negative result does not exclude the disease.

Clinical manifestations are protean and bizarre as a result of widespread vascular involvement, common symptoms are fever, nephritis, weakness, tachycardia, loss of weight, hematuria, polyneuritis, gastrointestinal symptoms, anemia, leukocytosis and eosinophilia^{223, 298}. Asthma may be a chief symptom^{355, 579}, in one such case painful swelling of both ankles was an early symptom⁵⁷⁹. "An eosinophilia, especially with a leukocytosis, in the presence of a rather bizarre symptomatology that does not seem to fit any syndrome should strongly suggest periarteritis nodosa. In one case the eosinophiles increased to 68 per cent of the leukocytes,³⁵⁵ but eosinophilia only occurs in about 12 per cent of cases. After onset of symptoms patients live an average of only 11 months²⁹⁸. But the disease is not always fatal. Four of Grant's seven patients were living after one to three years' observation. A few other cases, not cited here, were reported.

Disseminated Lupus Erythematosus An interesting symposium on this condition appeared^{310, 323, 416, 430, 515, 544}. Symptoms in 154 cases at the Mayo Clinic were analyzed. Arthralgia or arthritis was present in 20 per cent of 80 chronic cases, 57 per cent of 44 subacute cases, 63 per cent of 30 acute cases⁴¹⁶. Indeed the initial picture in this disease may be one of febrile polyarthritis easily mistakable for rheumatic fever. Two such cases were reported with necropsy data^{78, 215}. Joints were painful and swollen in six (40 per cent) of 15 new cases reported in 1940. Chief features of the disease are the skin lesions, sensitivity to light, articular symptoms, fever,

anemia, leukopenia (less than 4,500 leukocytes per cubic millimeter) and renal irritation

The articular symptoms are rarely diagnosed properly unless skin lesions are present and recognized. But joint symptoms often precede the skin lesions by 15 months to five years as they did in eight of Slocumb's 10 cases. The former resembled those of fibrositis, rheumatic fever, subacute or chronic rheumatoid arthritis, in one case actual destructive arthritis occurred.

[It is difficult to make a correct diagnosis from these articular and muscular symptoms if the skin lesion is not yet present. But a presumptive diagnosis of disseminated lupus erythematosus sometimes can be made in cases of "fibrositis," in which elevation of the sedimentation rate and leukopenia with or without renal irritation are present, or in cases of atypical "rheumatic fever" which is unresponsive to salicylates and is associated with leukopenia instead of the usual leukocytosis of rheumatic fever. In our experience such a tentative diagnosis has been confirmed in several cases by the subsequent appearance of the typical skin lesions. It is important to make such a diagnosis, for cases have been noted in which marked, even fatal, exacerbations have been precipitated by fever therapy, chrysotherapy, heliotherapy, etc. for supposed rheumatoid arthritis or rheumatic fever.—Ed.]

The pathology of skin (specific), renal and other lesions (nonspecific) was described^{310, 410, 514, 545}. A case of acute arthritis, associated with myocarditis, resembling acute lupus erythematosus was reported²²².

Treatment Chrysotherapy gave "very gratifying" results in chronic discoid lupus erythematosus⁴³⁰. Sulfanilamide was recommended by some,^{28, 503, 507} but since it increases some patients' sensitivity to light, O'Leary did not use it. Other remedies were discussed.

Libman-Sacks Syndrome In 1924 Libman and Sacks described what they regarded as a distinct syndrome: pleurisy with effusion, polyarthritis, leukopenia, especially a characteristic mural and valvular atypical verrucous endocarditis; two of their four patients had lupus erythematosus. Bunim's patient with disseminated lupus demonstrated this endocardial lesion. In eight of 23 hearts from patients with typical acute lupus erythematosus Gross found endocardial lesions similar to those in the cases of Libman and Sacks. Hence he concluded that the two conditions are closely related if not identical.

OTHER STUDIES ON JOINTS AND RELATED TISSUES

Articular Roentgenography In 70 per cent of normal persons menisci of the knee can be demonstrated by roentgenograms made with the knee in a position of forced adduction (Evans).

[The method is applicable only to patients without joint effusions. The "abnormal" case reported is not convincing.—Ed.]

Articular Physiology. Kelikian discussed the various components of joints and how they react to disease. Bowie attempted to summarize present knowledge of the physiology of articular tissues.

[The report was presented without sufficient coordination or critical evaluation. Most of the statements are correct, but no differentiation was made between well

founded conclusions and those based on little evidence, as, for instance, the discussion of the protective action of synovial fluid—Ed]

From a study of synovial fluid aspirated at death from 29 normal human knee joints, Coggeshall, Warren and Bauer determined the cytology of normal synovial fluid. The average cell count was 63 cells per cubic millimeter. The percentage and absolute number of cell types were 63 per cent, or 41.7 mononuclear phagocytes, 24.6 per cent or 14.7 lymphocytes, 6.5 per cent or 3.3 polymorphonuclear leukocytes, 4.3 per cent or 2.5 synovial cells and 2.2 per cent or 0.8 unidentified cells. Normal human synovial fluid is a dialysate of blood plasma containing albumin, globulin and mucin.⁴⁷⁷ The presence of mucin distinguishes synovial fluid and similar connective tissue fluids from other body fluids that are dialysates of plasma.

Further studies on the permeability of normal and inflamed synovial membranes were reported. Engel observed that all but five of 18 acid dyes entered the normal articular cavities of rabbits and cats following intravenous or intramuscular injection, whereas 10 alkaline dyes did not. Similar differences were observed in spinal and peritoneal fluids. He concluded that alkaline dyes are lipid soluble and therefore enter cells and are retained by them, never getting to the synovial barrier. Methyl orange (an acid dye that does not enter joints) is likewise lipid soluble.

[The differences reported were striking. However, the inconsistencies in the case of the 5 acid dyes are hard to explain. Furthermore these results contradict those of Tan (1935) who found that 16 of 26 alkaline dyes did enter joints. The results of the experiments with pronotosil did not corroborate what one of us, W. B., observed in inflamed human joints. Engel's interesting findings require confirmation and extension—Ed]

The absorption of uroselectan and potassium iodide from joints was found by Adkins and Davies to be radiographically complete in two hours. Absorption was not influenced by (1) motion or immobilization, (2) fluoride poisoning of the synovial membrane, (3) tying of lymphatics. Hence it was concluded that "true" solutions are removed from joints by diffusion to the blood stream, probably a predominantly physical process. The mechanism of removal of other substances from the subsynovial tissues varied with the size of the particle. Adkins and Davies believe that small colloidal particles are removed from joints like "true" solutions, but more slowly. When particles are more than a certain size, probably in the neighborhood of the size of the globulin molecule, removal by both blood capillaries and lymphatics ceases with the exception of the small quantities which enter the lymphatics. Larger particles, 100 microns or more, have no route of direct egress from subsynovial tissues. Shinkawa studied the time necessary for uranin (sodium fluorescein) to appear in urine after its injection into normal and experimentally inflamed joints. Its absorption from joints mildly inflamed with terepine oil was increased initially, after eight hours it was decreased below normal and absorption returned to normal in three weeks. Similar decreased absorption rates were noted in arthritides experimentally produced with staphylococci, *Escherichia coli* and *Bacillus pyocyaneus* (*Pseudomonas aeruginosa*) and in the case of intra-articular transplantation of a sarcoma.

King demonstrated that tissue cells of ganglia and cysts of menisci contain droplets of mucinoid material, which resemble the effects of cellular activity more closely than those of protoplasmic disintegration. The hypertrophied and extremely complex Golgi apparatus of these cells supports the view that the observed cytologic changes are due to cellular activity (secretion) rather than retrogression. King regarded ganglia and cysts of menisci as abnormal "joint spaces."

[The author's illustrations bear out his statements. This important work should be extended—Ed]

Further studies by Hills and Lutwak-Mann on the metabolism of articular cartilage confirm the previously reported experiments of Bywaters.⁵

The Silberbergs continued their studies on the growth of bone and cartilage, reporting on the effects of prolonged injections of bovine anterior pituitary extracts, undernutrition, and the combination of thyroidectomy and the administration of anterior pituitary extracts (bovine)

Experimental Infectious Arthritis Further work on the spontaneous polyarthritis of rats caused by pleuropneumonia-like organisms was reported by Collier and Staverman

They attempted to produce experimental arthritis in white rats by injecting synovial fluid, pericardial fluid and blood obtained from a patient with rheumatic fever. Long periods of incubation often ensued before arthritis finally developed. When it did, it was considered experimental, not spontaneous. They concluded that "an endogenous origin of the disease in the inoculated rats seems unlikely since white rats have not hitherto shown such changes."

[The authors apparently do not realize that "normal" white rats are frequently infected with pleuropneumonia-like organisms. Therefore much significance cannot be attached to arthritis "induced" in rats by injecting body fluids from patients with rheumatic fever. The arthritis in the rats was probably spontaneous, not experimental.—Ed.]

An excellent account of the naturally occurring and experimentally produced polyarthritis of swine due to an erysipelotheix organism was presented by Collins and Goldie who pointed out its many clinical, serologic and pathologic similarities to human rheumatoid arthritis.

Extensive pathologic and bacteriologic studies were made by Collins and Goldie on nine swine which had natural chronic proliferative polyarthritis of swine due to swine erysipelas. The disease was reproduced experimentally in other swine by intravenous, but not subcutaneous, injections of *Erysipelothrix rhusiopathiae*. Many grossly arthritic joints were sterile. A state of hypersensitivity was not essential for the production of arthritis. Specific agglutinins were not always found in high titer. Comparisons were made between the swine arthritis and human chronic arthritis. The experiments suggested that articular inflammation may continue after infecting organisms disappear. Such a behavior of joint tissues may reconcile the chronicity of human rheumatoid arthritis with the sterility of joints. Perhaps rheumatoid arthritis results from the localization of bacteria in joints after a transient bacteremia, and these bacteria start tissue reactions which continue chronically even after the infecting germs are destroyed. Serologic tests on humans seemed to indicate that human rheumatoid arthritis is not caused by the infection of swine erysipelas.

An acute septic polyarthritis resulted in 45 of 51 albino rats when Rothbard injected Group A hemolytic streptococci isolated from a case of human septicemia.

[The author believed this to be the first account of hemolytic streptococcal arthritis in rats.—Ed.]

Experimentally produced infectious arthritis was treated with various chemotherapeutic agents. Heilman reported that a single injection of gold sodium thiomalate (myochrysine) protected mice against fatal doses of *Streptobacillus moniliformis* whereas neoparsphenamine and sulfapyridine were ineffective. It was proved that gold salts can prevent arthritis from hemolytic streptococci,¹⁵⁴ also that from pleuropneumonia-like organisms in rats.¹⁵⁵ Sabin and Warren obtained similar results with

two insoluble gold compounds (calcium aurothioglycolate and calcium aurothiomalate) in experimental arthritis in mice caused by a pleuro-pneumonia-like organism

Palcopathology Students of rheumatism will be interested in Hormell's notes on the history of rheumatism and gout

Physiology of Muscles To give hypertonic saline solution intravenously is the only method which will increase the temperature of both skin and muscles, according to Friedlander and his colleagues. Blood flow in muscles of extremities is not directly controlled by the sympathetic nervous system. Investigators can no longer conclude that increased circulation in skin is accompanied by an increased circulation in muscle.

[This paper would have been of more importance had not the subjects all had peripheral vascular disease. A few patients had unilateral vascular disease, but the reader is given no clue as to their identity—Ed.]

RHEUMATISM AND THE WAR

British Experiences The incidence of rheumatic diseases in peace time has been fairly high in the British army and even higher in the civil population. Copeman and Horde²⁸⁰ considered it extremely unlikely that the incidence of rheumatic diseases among British soldiers and civilians would be lowered in war time. Indeed under the latter circumstances which inevitably involve an increase in exposure, nutritional deficiencies and other factors, the incidence would be expected to rise. Copeman [who as major was in charge of a rheumatism center in France with the British Expeditionary Forces in 1940—Ed.] reported that during the first 4 months of the present war "rheumatic cases" comprised 15 per cent of the total admissions, 26 per cent of all medical admissions, to No. 3 General Hospital. Similar figures were reported from No. 2 General Hospital. Of the first 100 cases studied 15 per cent were of rheumatic fever, 6 per cent were of rheumatoid arthritis, 9 per cent were of osteo-arthritis (generally traumatic), 70 per cent were of fibrositis. The average age of the patients was 29.6 years. "If these figures be taken as representing a fair picture of the incidence of 'rheumatism' in the B. E. F., it follows that there will be at any time 12 to 15 per cent of such cases in every hospital although this may show some seasonal variation." The great problem will be to secure adequate treatment for all these patients, most of whom should thereby be capable of being returned to duty.

Rheumatologists in the War Only recently has the medical profession in Great Britain studied the problems of rheumatism closely, hence the number of practitioners interested therein is small. It was Horde's belief that in the army their skill should be concentrated so far as possible on the management of rheumatic diseases, that their energies could be best conserved by the establishment of special military and nonmilitary rheumatism centers, from which some could go out as traveling consultants, that these rheumatologists would be best qualified to carry on needed researches, weed out malingerers in the military services and give authoritative opinions.

regarding the fitness of recruits suspected of having, or being liable to, the rheumatic diseases Horder further recommended that the British army, navy and air force should each have rheumatism units attached to their training centers and hospitals These views were shared by the writer of an editorial¹⁷⁰ who stressed the superior qualifications of the rheumatologist in diagnosing and treating the confusing diseases of muscles and joints he best knows the value of this and that remedy "The most useful contribution rheumatologists can make to the war effort is to bring this experience to bear on joint diseases as a whole It may be that war will achieve in a few years what under peace conditions might have taken a few generations—the recognition of arthrology as a specialty, and the merging of 'rheumatology' with it"

Some of the special medical knowledge that rheumatologists should have in war time, and which they can help to advance, has been touched on here and there in this Review, of chief importance are the newer advances in the treatment of septic arthritis³³ and septic lesions from penetrating war wounds in and near joints^{94, 187, 588} The interesting studies of Stott and Copeman on articular symptoms from epidemic meningococcemia among soldiers and of Bennett and Copeman on rheumatic symptoms associated with rubella among soldiers have been mentioned Our next Review doubtless will contain much more of these special data

Physical Therapy and War The special importance of physical therapy and the rôle of physical therapists in war times was discussed^{196, 220, 307, 518}

One of the outstanding lessons of the first world war concerned the great importance which physical therapy played in the rehabilitation of war wounds The belated recognition of this fact resulted in needless suffering and disability Early physical treatment could have reduced greatly the pension costs of disabled soldiers The "reservicing" of casualties requires trained professional and technical personnel and adequate equipment The organization of physical therapy for war time needs should be in the hands of those who have made it a special study It was recommended that a Director of Physical Therapy be appointed to render service to the Ministry of Health The director should head a central organization to be responsible for (1) the creation of a central register of those qualified in physical therapy, (2) the enlistment of qualified specialists for military and special civil duties, (3) the correlation of their work with those in all other branches of service, (4) an adequate supply of technical personnel to manufacture and keep in repair sufficient apparatus, (5) the control and distribution of all available apparatus, (6) the formation of large physical therapy units in certain base hospitals and smaller units to be made temporarily available to other base or field hospitals as necessary, (7) the continued training of personnel so that efficient surgical and medical teams may be kept available for remedial work The special value of occupational therapy in military hospitals also was stressed²⁷

As a result of such advice facilities for physical medicine were organized (May, 1939) by the Ministry of Health under the Emergency Hospital Scheme with Sir Robert Woods⁶¹⁰ as consultant adviser in physical medicine to the Ministry of Health Eleven more or less autonomous administrative regions were established in England and Wales, the London region being divided into 10 sectors In each sector is a specialist in physical medicine These specialists constitute the "Medical Per-

sonnel' The "Auxiliary Personnel" comprises 6,000 members of the Chartered Society of Massage and Medical Gymnastics who have volunteered for war service and have been classified as to experience, seniority, etc. The "Equipment Personnel" is responsible for the production and maintenance of needed apparatus of which two simple agents were of preëminent value (1) various methods for producing heat and (2) electrical currents to stimulate muscle contractions. This personnel is also responsible for space facilities. Under this scheme physical therapy is available for rheumatic patients at all Emergency Medical Hospitals with more than 300 beds⁴¹⁰

For the application of physical therapy to rheumatic soldiers in mobile hospitals, evacuation centers or base hospitals without adequate electricity simple nonelectrical methods are required. Several simple methods were improvised by Copeman:

They included a steam bath made up of two towel rails on three sides of an ordinary canvas chair, the whole being covered with layers of sacking under which steam was led through a rubber tube attached to a large tin or kettle boiling on a primus stove, a radiant heat lamp made out of two petrol tins with a sheet of metal behind to act as a reflector, the source of heat being a plate of cast iron or a bundle of gas "elements" placed over a primus stove and allowed to glow to a dull red.

[For his ingenuity and enterprise in devising such methods to apply physical therapy under the difficult circumstances of war Copeman was just awarded the gold key of the American Congress on Physical Therapy, an award also made to three distinguished Americans—Ed.]

American Preparedness. At the request of the Surgeon General's office, U. S. Army, the American Rheumatism Association has canvassed its members as to their willingness and qualifications for special military service. Groups of senior and junior medical and orthopedic consultants on rheumatic diseases have been established provisionally and data thereon have been transmitted to the Surgeons General of the Army, Navy and Public Health Department. A brief synopsis on the diagnosis and treatment of the common rheumatic diseases has been prepared to be disseminated from the Surgeon General's office as a circular letter to all medical officers in the Army.* American physical therapy consultants and technicians are likewise being mobilized and a primer on the simpler methods of applying physical therapy is in preparation. Coulter¹³⁸ and others have discussed the place of physical therapy in the American military service. Physical standards set up for the selection of soldiers under selective service include data on the relative disablement caused by residual or active rheumatic diseases⁴⁰¹

THE CAMPAIGN AGAINST RHEUMATISM

There are three chief goals to be accomplished by the campaign against rheumatism: (1) reduction of the general incidence of the rheumatic diseases by providing better housing and nutrition for the poorer classes, decreasing the industrial hazard provided by exposure to cold and damp and reducing the trauma of industrial work, (2) expansion of existing hospital facilities and convalescent homes through the cooperation of Departments of Public Health, (3) expansion of educational facilities to both laymen and the medical profession (Pemberton and Scull).

Stressed was the need for more British and American hospital facilities. Davidson reported that in Scotland about 1,000 persons with chronic rheu-

* This is scheduled to appear in the Army Medical Bulletin, January, 1942.

matic diseases were treated annually as in-patients in 10 large voluntary hospitals, as compared to 5,000 out-patients. Only a minority of Scottish rheumatic sufferers were receiving adequate treatment. Each piece of physical therapy apparatus was in constant use, each masseuse gave an average of 6,000 treatments. "Since only one of every 100 patients suffering from the severer forms of chronic rheumatic disease is admitted to the voluntary hospitals and since only one of every 20 patients obtains physical therapy, it is clear that no real progress can be made until additional facilities are available. The serious nature of the finances of the large voluntary hospitals in Scotland makes it extremely unlikely that they can erect additional facilities. Hence while the voluntary hospitals must continue to take an active share in the fight against rheumatic diseases, the magnitude of the problem necessitates a national campaign so that local authorities will provide, in selected areas, centers for diagnosis and treatment."¹⁴⁹ This lack of proper facilities in Great Britain was called a "national scandal."²⁷⁸

In the United States also arthritis is "a neglected disease" according to Snyder. Arthritic victims lacking the means to finance treatment are almost entirely dependent on the resources of private hospitals and physicians. Most general hospitals consider arthritic patients a nuisance. In the entire United States there is no hospital or institution devoted exclusively to the treatment of arthritis. Very few private hospitals with special facilities for arthritics can treat or hospitalize their patients free of charge. There are 100,000 free beds and over \$100,000,000 available for the care of, and research in, tuberculosis. But there are not more than 200 free beds available for indigent arthritics and not more than \$200,000 available for research projects to combat the scourge of rheumatism.

Physicians and medical students should be constantly informed as to the extent of the problem, trends of new research and the real value of early diagnosis and treatment.^{155, 418} But from past experiences in other crusades against chronic disease, it is known that the medical profession, no matter how outstanding its men, brilliant their research and high their ideals, can accomplish little by itself. The profession can only succeed by arousing the public against the scourge of rheumatism.⁵²⁴ In the mind of the public must be created a desire for early diagnosis and adequate treatment. If private hospitals cannot provide the latter, an aroused public opinion will guarantee it if necessary by creating subsidized institutions. "The problem should be turned into a project" and physicians as leaders in national welfare are the best group to undertake the project, they should not wait until a public or political solution is thrust on them.²³⁷

The rôle of local authorities in the fight against rheumatism was outlined in the scheme of the Kensington Borough Council (England)¹⁹¹ which made rheumatic fever a reportable disease and established the first municipal rheumatism clinic in Great Britain. Local authorities should publicize the existing treatment facilities within their area, introduce poor rheumatic patients

early to treatment centers, inquire into the environmental conditions (dampness, overcrowding) of rheumatic victims, attempt to remedy unsuitable housing conditions, compile statistics on the rheumatic diseases, educate the public with regard to the campaign against rheumatism, and provide antidotes for the fraudulent claims of quacks

In England the campaign is led by Lord Horder, Chairman of the Empire Rheumatism Council who has published "A plan for national action" which made many specific recommendations. It is stimulating to read the Third and Fourth Annual Reports of the war time activities of the Empire Rheumatism Council.¹⁻⁴ Despite the extreme urgencies of war the Council decided to carry on its diverse activities as far as possible. The war has curtailed the Council's researches only slightly, its facilities for treatment more notably. Certain treatment centers were temporarily closed; one of the Council's laboratories was destroyed by bombs, the evacuation of large numbers of school children interrupted the London County Council's scheme for the prevention and treatment of rheumatic diseases. Despite these difficulties many of the Council's therapeutic and research activities have continued, special projects to improve treatment facilities for rheumatic victims in the fighting forces have been undertaken. Meanwhile the Council has sought to conserve its resources for the time after the war when the inevitable harvest of postwar cripples will need its services. But today's problems must not be neglected even in these troubled times. "Clear thinking will bring the conclusion that the sound way to meet the stress of difficult times is to avoid waste. It is a tragic waste of man-power and of money to allow rheumatic diseases to exact its present heavy toll on our people. Nor should it be forgotten that national security has its firmest foundation in a healthy, contented community."²⁸⁰

If the embattled and harassed British Medical profession refuses even to slacken its campaign against rheumatism can American physicians, even though they too are now at war, dare to do other than redouble their efforts?

REFERENCES

- 1 *First Rheumatism Review* HENCH, P S, BAUER, WALTER, FLETCHER, A A, GHRIST, DAVID, HALL, FRANCIS, and WHITE, PRESTON. The present status of the problem of "rheumatism", a review of recent American and English literature on "rheumatism" and arthritis, *ANN INT MED*, 1935, viii, 1315-1374, 1495-1555, 1673-1697
- 2 *Second Rheumatism Review* HENCH, P S, BAUER, WALTER, FLETCHER, A A, GHRIST, DAVID, HALL, FRANCIS, and WHITE, T P. The present status of the problem of "rheumatism" and arthritis, review of American and English literature for 1934, *ANN INT MED*, 1936, ix, 883-982
- 3 *Third Rheumatism Review* HENCH, P S, BAUER, WALTER, FLETCHER, A A, GHRIST, DAVID, HALL, FRANCIS, and WHITE, T P. The problem of rheumatism and arthritis, review of American and English literature for 1935, *ANN INT MED*, 1936, x, 754-909
- 4 *Fourth Rheumatism Review* HENCH, P S, BAUER, WALTER, GHRIST, DAVID, HALL, FRANCIS, HOLBROOK, W P, KEY, J A, and SLOCUMB, C H. The present status of

rheumatism and arthritis, review of American and English literature for 1936, *ANN INT MED*, 1938, xi, 1089-1247

- 5 *Fifth Rheumatism Review* HENCH, P S, BAUER, WALTER, DAWSON, M H, HALL, FRANCIS, HOLBROOK, PAUL, and KEY, J A The problem of rheumatism and arthritis, review of American and English literature for 1937, *ANN INT MED*, 1939, xii, 1005-1104, 1295-1374
- 6 *Sixth Rheumatism Review* HENCH, P S, BAUER, WALTER, DAWSON, M H, HALL, FRANCIS, HOLBROOK, W P, KEY, J A, and McEWEN, CURRIER The problem of rheumatism and arthritis, review of American and English literature for 1938, *ANN INT MED*, 1940, xiii, 1655-1739, 1837-1990
- 7 *Seventh Rheumatism Review* HENCH, P S, BAUER, WALTER, DAWSON, M H, HALL, FRANCIS, HOLBROOK, W P, KEY, J A, and McEWEN, CURRIER The problem of rheumatism and arthritis, review of American and English literature for 1939, *ANN INT MED*, 1941, xiv, 1383-1448, 1631-1701
- 8 ABRAMS, N R, and BAUER, WALTER The treatment of rheumatoid arthritis with sulfur, a critical evaluation, *New England Jr Med*, 1940, ccxii, 541-546
- 9 ADAMS, Z B Tuberculosis of the spine in children A review of sixty-three cases from the Lakeville State Sanatorium, *Jr Bone and Joint Surg*, 1940, xxii, 860-861
- 10 ADKINS, E W O, and DAVIES, D V Absorption from the joint cavity, *Quart Jr Exper Physiol*, 1940, xxx, 147-154
- 11 ALBRIGHT, FULLER, BLOOMBERG, ESTHER, and SMITH, PATRICIA H Post-menopausal osteoporosis, *Trans Assoc Am Phys*, 1940, lv, 298-305
- 12 ALBRIGHT, P M, and METCALFE, E E Treatment of gonococcal infection with sulfa-pyridine, seventy ambulatory cases treated aboard ship, *U S Naval Med Bull*, 1940, xxxviii, 563-572
- 13 ALEXANDER, J C, FORBES, M A, and HOLLOMAN, A L The use of sulfanilyl-sulfanilamide (disulon) in the treatment of sulfanilamide-resistant gonorrhea in the male, *Am Jr Syph, Gonorr and Ven Dis*, 1940, xxiv, 234-246
- 14 ALLBRITTEN, F F, SHEELY, R F, and JEFFERS, W A Haverhillia multiformis septi-cemia, its etiologic and clinical relationship to Haverhill and rat-bite fevers, *Jr Am Med Assoc*, 1940, cxiv, 2360-2363
- 15 ALTSCHULE, M D, and BUDNITZ, EDWARD Rheumatic disease of the tricuspid valve, *Arch Path*, 1940, xxx, 7-25
- 16 AMBERSON, J B, JR Pathogenesis and medical treatment of tuberculosis of the vertebrae, *Jr Bone and Joint Surg*, 1940, xxii, 807-814
- 17 ANDERSON, N L, and PALMER, W L The danger of gold salt therapy, report of fatal case, *Jr Am Med Assoc*, 1940, cxv, 1627-1630
- 18 ANDERSON, R L Isolated tuberculosis of the spinous process of a vertebra, report of a case, *Jr Bone and Joint Surg*, 1940, xxii, 741-744
- 19 ANGLINE, D M, and ROTHBARD, SIDNEY The significance of the synovial villus and the ciliary process as factors in the localization of bacteria in the joints and eyes of rabbits, *Jr Exper Med*, 1940, lxxi, 129-136
- 20 ANGIE, F E, and ANGIE, W H The treatment of acute and chronic brucellosis, *J Kansas Med Soc*, 1940, xli, 233-236
- 21 BACH, FRANCIS, and SAVAGE, OSWALD Splenectomy in the treatment of rheumatoid arthritis, a report of three cases, *Ann Rheumat Dis*, 1940, ii, 47-57
- 22 BACH, T F Focal infection and arthritis, *Med Clin North America*, 1940, xxiv, 1673-1681
- 23 BARNES, N H, and BARNARD, ELEANOR Short-wave diathermy, *Med Bull Vet Admin*, 1940, xii, 31-32
- 24 BAILEY, J E Rheumatic infection in children in the deep South, *New Orleans Med and Surg Jr*, 1940, xciii, 240-244
- 25 BATE, DAVID M Gonococcal rheumatism, *Brit Jr Rheumatism*, 1940, ii, 208-211

- 26 BAKER, G. S. and SONIAT, T. L. L. Removal of midline protrusion of an intervertebral disk to relieve backache which caused total disability presentation of case, *Proc Staff Meet Mayo Clin*, 1940, **xx**, 280-282
- 27 BAUMINGER, E. G., McDONALD, H. P., and COILMAN, R. C. Sulfathiazole in the treatment of gonorrhea, a preliminary report, *South Med Jr*, 1940, **xxxiii**, 911-913
- 28 BARMER, H. W. Lupus erythematosus the effects of sulphonamides, *Lancet*, 1940, **i**, 583-586
- 29 BARTIS, W. P. The surgical treatment of acute subacromial bursitis, *Jr Bone and Joint Surg.* 1940 **xxii**, 120-121
- 30 BAUCKUS, H. H., and KWAK, A. V. Psoriasis—what to do about it, *New York State Jr Med* 1940, **xl**, 96-100
- 31 BAUER, WALTER, and SHORT, C. L. The treatment of the arthritides of known origin, *New England Jr Med*, 1940, **ccxxviii**, 286-293
- 32 BLANCHAMP, F. G. Manipulation of the dorsal vertebrae, *Rheumatism*, 1940, **ii**, 36-38
- 33 BRIDMAN, FINWICK, and SULLIVAN, J. E. Blood-borne pyogenic infections of bones and joints, *Ann Surg*, 1940, **cxv**, 292-314
- 34 BRID, I. R. Drainage of chronic foci of infection in the mouth and throat, a preliminary report, *Jr Med Soc New Jersey*, 1940, **xxvii**, 349-355
- 35 BRILL, B. T. The prevention and correction of deformities in arthritis, *Med Clin North America*, 1940, **xxv**, 1735-1743
- 36 BRILL, B. T. The diagnosis and treatment of low back pain, *Med Clin North America*, 1940, **xxv**, 1755-1766
- 37 BRILL, CHARLOTTE, and SWAIN, L. T. Occupational therapy in arthritis, *Public Health Nursing*, 1940, **xxvii**, 243-245
- 38 BRILL, J. C. The roentgen-ray examination in individuals suffering from low back and sciatic pain, with examples of some lesions in which errors in diagnosis may readily be made, *Radiology*, 1940, **xxv**, 449-458
- 39 BRILLHOUSE, HEIFEN W. Chronic brucellosis, report of two cases in children diagnosed by intracutaneous tests, *Jr Med Assoc Georgia*, 1940, **xxix**, 260-264
- 40 BRILL, E. and FOLKENBERG, A. W. Gonorrhea its treatment by artificial fever, and by fever therapy in combination with sulfanilamide, *California and West Med*, 1940, **liii**, 169-172
- 41 BRILL, ELMER, and FOLKENBERG, A. W. Treatment of gonorrhea by artificial fever alone and in combination with sulfanilamide, *Arch Phys Therap*, 1940, **xxi**, 203-210
- 42 BRINNITT, G. A., ZELLER, J. W., and BAUER, WALTER. Subcutaneous nodules of rheumatoid arthritis and rheumatic fever, a pathologic study, *Arch Path*, 1940, **xxx**, 70-89
- 43 BENNETT, R. A., and COPEMAN, W. S. C. Notes on rubella with special reference to certain rheumatic sequelae, *Brit Med Jr*, 1940, **i**, 924-926
- 44 BERENS, S. N. Lipiodol versus air—as an aid in diagnosis of protrusion of intervertebral disc, *Northwest Med*, 1940, **xxxix**, 160-163
- 45 BERG, CARL. Intrapelvic protrusion of the acetabulum, *Surg Clin North America*, 1940, **xx**, 863-867
- 46 BERG, H. W. Sulfanilyl sulfanilamide (disulon) in the treatment of gonococcal urethritis and its complications, *Am Jr Syph, Gonorr and Ven Dis*, 1940, **xxiv**, 337-343
- 47 BERGHAUSEN, OSCAR. Fatal leukopenia following internal administration of causalin, *Jr Am Med Assoc*, 1940, **cxiv**, 1547-1548
- 48 BERRY, M. G. Cinchophen poisoning, *Jr Kansas Med Soc*, 1940, **xli**, 337-339
- 49 BETHEA, O. W. Rheumatic fever, *Internat Med Digest*, 1940, **xxxvi**, 114-119
- 50 BETHEA, O. W. Atrophic arthritis, *Internat Med Digest*, 1940, **xxxvi**, 172-175
- 51 BLACK, J. R. Senile osteoporosis of the spine, *Proc Staff Meet Mayo Clin*, 1940, **xi**, 619-623
- 52 BLACK, W. C. Synovoma (synovialoma) of the foot, report of a case, *Am Jr Cancer*, 1940, **xxxix**, 199-206

- 53 BLAISDELL, E R Skin testing for undulant fever in Maine, results obtained in five hundred unselected hospital patients, Jr Maine Med Assoc, 1940, xxxi, 85-86
- 54 BLOCK, W D, and BUCHANAN, O H The microdetermination of gold in biological fluids, Jr Biol Chem, 1940, cxxxvi, 379-385
- 55 BLUE, W R Brucellosis, with report of cases, Jr Tennessee Med Assoc, 1940, xxxiii, 9-22
- 56 BOAS, E P, and ELLENBERG, MAX Rheumatic pericarditis with effusion treated with salicylates, Jr Am Med Assoc, 1940, cxv, 345-348
- 57 BOISVERT, P L The streptococcal antifibrinolysin test in clinical use, Jr Clin Invest, 1940, xix, 65-74
- 58 BORTS, I H Etiology and laboratory diagnosis of brucellosis, Jr Iowa Med Soc, 1940, xxx, 254-256
- 59 BOSWORTH, D M An analysis of twenty-eight consecutive cases of incapacitating shoulder lesions, radically explored and repaired, Jr Bone and Joint Surg, 1940, xxii, 369-392
- 60 BOWERS, R F Hyperparathyroidism, Internat Clin, 1940, s 3, iii, 277-284
- 61 BOWIE, M A The physiology of joint tissue, Med Clin North America, 1940, xxiv, 1621-1632
- 62 BOYD, L J I The clinical aspects of periarteritis nodosa, Bull New York Med Coll, Flower & Fifth Ave Hosps, 1939, i, 219-225, II The clinical aspects of periarteritis nodosa, 1940, iii, 32-40, III Periarteritis nodosa Cutaneous symptoms, 175-182, IV Periarteritis nodosa Neuromyositic manifestations, 272-279
- 63 BRADLEY, W B, and IVY, A C Excretion and determination of cinchophen in bile, Proc Soc Exper Biol and Med, 1940, xlv, 143-148
- 64 BRFAZEALF, E L, and GRFFNF, R A Incidence of agglutinins for typhoid, paratyphoid and Brucella abortus, Southwestern Med, 1940, xxiv, 119-121
- 65 BRICKEY, P A, and GROW, J B Osteochondritis dissecans, report of cases involving elbow, ankle and metatarsophalangeal joints, Am Jr Surg, 1940, xlviii, 463-466
- 66 BRITTON, R H The National Health Survey, receipt of medical services in different urban population groups, Pub Health Rep, 1940, lv, 2199-2224
- 67 BRITTON, R H, COLLINS, S D, and FITZGERAID, J S The National Health Survey, some general findings as to disease, accidents, and impairments in urban areas, Pub Health Rep, 1940, lv, 444-470
- 68 BRØCHNER-MORTENSEN, KNUD The uric acid content in blood and urine in health and disease, Medicine, 1940, xix, 161-229
- 69 BROOKF, J A Orthopedic management of hypertrophic arthritis, Hahnemann Monthly, 1940, lxxv, 277-282
- 70 BROWN, C H Foci of infection in psychiatric patients, Am Jr Med Sci, 1940, cxcix, 539-545
- 71 BROWN, M G, and WOLFF, L Recovery from acute rheumatic fever without permanent cardiac damage, New England Jr Med, 1940, ccxxiii, 242-243
- 72 BRUCE, J G, and CASWELL, M Precipitin reactions in rheumatoid arthritis, Jr Lab and Clin Med, 1940, xxvi, 464-467
- 73 BRUITSCH, W L Chronic rheumatic brain disease as a possible factor in the causation of some cases of dementia praecox, Am Jr Psychiat, 1940, xcvi, 276-296
- 74 BRUMBAUGH, H L Calcifying tendinitis traumatica, diagnosis and treatment of post-traumatic changes in and about joints, Am Jr Surg, 1940, xlviii, 681-684
- 75 BRUNFT, W M, REINHARDT, C H, and SHAW, N D Treatment of gonorrhea in the male with sulfamidamyl and urethral injections of acriflavin, Virginia Med Monthly, 1940, lxxii, 40-44
- 76 BRUNFT, W M, SAMBERG, J B and KOCH, R A The treatment of gonococcal infection in women, a comparison of the results with and without sulfamidamide therapy, New England Jr Med, 1940, ccxxiii, 277-279

- 77 BUST, T P, and SIMON, R H Intensive treatment of gonorrhoea with M & B 693, *Jr Roy Army Med Corps*, 1940, **xxiv**, 229-231
- 78 BUNIM, J J Lupus erythematosus disseminatus, *ANN INT MED*, 1940, **xiii**, 1399-1413
- 79 BUNIM, J J, and MCLWEN, CURRIER The antistreptolysin titer in rheumatic fever, arthritis and other diseases, *Jr Clin Invest*, 1940, **xix**, 75-82
- 80 BUNIM, J J, and MCLWEN, CURRIER Tophus of the mitral valve in gout, *Arch Path*, 1940, **xxix**, 700-704
- 81 BUNTS, A T Retropulsion of ruptured nucleus pulposus simulating tumor of the cauda equina, report of a case, *Cleveland Clin Quart*, 1940, **vii**, 257-260
- 82 BURNETT, E J Diathermy in arthritis, *Med Bull Vet Admin*, 1940, **xvii**, 23-27
- 83 BUTTON, MARTIN Muscular rheumatism, local injection treatment as a means of rapid restoration of function, *Brit Med Jr*, 1940, **ii**, 183-185
- 84 Cabot case 26231 Acute and chronic rheumatic heart disease with mitral and aortic stenosis, *New England Jr Med*, 1940, **ccxxii**, 966-972
- 85 CAFFEY, JOHN, and SCHLESINGER, E R Certain effects of hemophilia on the growing skeleton, some roentgenographic observations on overgrowth and dysgenesis of the epiphyses associated with chronic hemarthrosis, *Jr Pediat*, 1940, **xvi**, 549-565
- 86 CAIDER, R M Modification of Huddleson's opsonocytophagic reaction, *Jr Lab and Clin Med*, 1940, **xxi**, 769-770
- 87 CAIHOUN, O V Rheumatic heart disease, *Nebraska Med Jr*, 1940, **xxv**, 56-57
- 88 CAMP, J D The roentgenologic diagnosis of intraspinal protrusion of intervertebral disks, *Minnesota Med*, 1940, **xxiii**, 688-692
- 89 CAMP, J D, and ADDINGTON, E A Intraspinal lesions associated with low back pain and sciatic pain, and their localization by means of lipiodol within the subarachnoid space, *Radiology*, 1939, **xxviii**, 701-708
- 90 CAMP, P D Some points in the differential diagnosis of rheumatic and syphilitic heart disease, *South Med and Surg*, 1940, **cxii**, 367-370
- 91 CAMPBELL, A M G Carcinomatosis of bone, difficulties in diagnosis, *Lancet*, 1940, **i**, 777-780
- 92 CAMPBELL, W C Interposition of vitalium plates in arthroplasties of the knee, preliminary report *Am Jr Surg*, 1940, **xlvi**, 639-641
- 93 CANBY, C P Oral infection in arthritis, *Mil Surgeon*, 1940, **lxxxvi**, 355-363
- 94 CANTLIE, N An analysis of knee joint operations, *Jr Roy Army Med Corps*, 1940, **lxvi**, 69, 141
- 95 CARY, E J Low back pain, a symposium 1 Anatomical aspect, *Wisconsin Med Jr*, 1940, **xxix**, 427-446
- 96 CARPENTER, C M, and WESTPHAL, R S The problem of the gonococcus carrier, *Am Jr Pub Health*, 1940, **xxx**, 537-541
- 97 CARRELL, BRANDON, and CHIDRESS, H M Osteochondritis dissecans of a metatarsal head, *Jr Bone and Joint Surg*, 1940, **xxii**, 442-443
- 98 CARRUTHERS, F W Synovectomy of the knee joint, *South Med Jr*, 1940, **lxviii**, 550-552
- 99 CASTELLANI, ALDO, and GIROLAMI, MARIO Febrile hepato-splenomegaly with arthritis, *Jr Trop Med*, 1940, **xliii**, 1-4
- 100 CAWADIAS, A P Sulphur treatment in endocrine metabolic arthropathies, *Brit Jr Rheumat*, 1940, **ii**, 125-129
- 101 CECIL, R L The therapy of rheumatic fever, *Jr Am Med Assoc*, 1940, **cxiv**, 1443-1447
- 102 CECIL, R L Present trends in the study of arthritis and rheumatism, *Proc Staff Meet Mayo Clin*, 1940, **v**, 556-560, *Minnesota Med*, 1940, **xxiii**, 533-542
- 103 CECIL, R L Physical therapy compared with other measures in arthritis, *Arch Phys Therap*, 1940, **xxi**, 581-584
- 104 CHAMBERLAIN, W E, and YOUNG, B R Air myelography in the diagnosis of intraspinal lesions producing low back and sciatic pain, *Radiology*, 1939, **xxxiii**, 695-700

- 105 CHANDLER, F A, and PAGE, M A Tuberculosis of the spine, end-result series studied at Children's Memorial Hospital, Chicago, Jr Bone and Joint Surg, 1940, xxii, 851-859
- 106 CHANEY, W C The treatment of atrophic arthritis, Memphis Med Jr, 1940, xv, 187-188
- 107 CHENEY, GARNETT Effect of diet and cinchophen on production of experimental gastric ulcers in chicks, Proc Soc Exper Biol and Med, 1940, xlv, 190-195
- 108 CHINN, A B Treatment of undulant fever with sulphanilamide, case report, ANN INT MED, 1940, xiv, 921-924
- 109 CLAHR, JACOB, KLEIN, M D, and GREENSTEIN, N M Rheumatic heart disease in pregnant women, treatment in a city hospital, New York State Jr Med, 1940, xl, 1242-1247
- 110 CLAIBORNE, T S Gout in a seventeen year old girl, Jr Am Med Assoc, 1940, cxv, 38-39
- 111 CLARKE, G E Treatment of psoriasis with concentrated viosterol, Arch Dermat and Syph, 1940, xli, 664-666
- 112 CLARKE, P J H The clinical and public health aspects of juvenile rheumatism in Dublin, Irish Jr Med Sci, 1940, 97-118
- 113 CLAWSON, B J Rheumatic heart disease, an analysis of 796 cases, Am Heart Jr, 1940, xx, 454-474
- 114 CLEVELAND, MATHER Treatment of tuberculosis of the spine, Jr Bone and Joint Surg, 1940, xxii, 824-839
- 115 COBURN, A F Faulty disposal of Streptococcus hemolyticus in relation to development of rheumatic lesion (Mary Scott Newbold lecture), Trans and Stud Coll Physicians Philadelphia, 1940, viii, 91-104
- 116 COBURN, A F, and MOORE, LUCILLE V The prophylactic use of sulfanilamide in rheumatic subjects, Med Clin North America, 1940, xxiv, 633-638
- 117 COE, MEYERON, and SILVERS, S H Ehlers-Danlos syndrome (cutis hyperelastica), Am Jr Dis Child, 1940, lx, 129-135
- 118 COGGESHALL, H C, WARREN, C F, and BAUER, WALTER The cytology of normal human synovial fluid, Anat Rec, 1940, lxxvii, 129-144
- 119 COHEN, ABRAHAM, DUBBS, A W, and MYERS, ABRAHAM The treatment of atrophic arthritis with estrogenic substance, New England Jr Med, 1940, ccxxxii, 140-142
- 120 COHEN, ABRAHAM, and ROSEN, HARRY Mecholyl and histamine effects on peripheral circulation and relief of arthritic pain, Arch Phys Therap, 1940, xxi, 12-16
- 121 COHEN, IRA Calcified protruded intervertebral disc, Jr Mt Sinai Hosp, 1940, vi, 255-258,
- 122 COKKINIS, A J Gonococcal rheumatism, Rheumatism, 1940, ii, 39-43
- 123 COLBERT, W C Social and economic aspects of arthritis, Memphis Med Jr, 1940, xv, 179-181
- 124 COLF, B L, and MOORE, MOORE, JR Caisson disease with special reference to the bones and joints, report of two cases, Ann Surg, 1940, cxv, 1065-1075
- 125 COLLIER, W A, and STAVELMAN, G J The spontaneous polyarthritis of rats and the syndrome induced by inoculation of human material in these animals, Ann Rheumat Dis, 1940, ii, 58-66
- 126 COLLINS, D H, and GOLDF, WILLIAM Observations on polyarthritis and on experimental Erysipelothrix infection of swine, Jr Path and Bact, 1940, 1, 323-353
- 127 COMBES, F C, DITTRICH, CARISLE, and COHEN, JULIUS Keratosis blennorrhagica, a brief review and report on the effects of hyperpyrexia in its treatment, Jr Am Med Assoc 1940, cxiv, 2078-2082
- 128 COMPTON, E I Syphilis of the bones and joints, Urol and Cutan Rev, 1940, xlv, 535-540
- 129 COMPTON, B I Role of the dentist in arthritis Jr Am Dent Assoc, 1940, lxvii, 1209-1213
- 130 COOPER, A H, and MURPHY, D S Atrophic Charcot's hips report of five cases, Jr Bone and Joint Surg, 1940, xxii, 638-644

- 131 COOMBS, I S Clinical gout, Ohio State Med J, 1940, xxvi, 951-954
- 132 COOMBS, I S, PFCORA, L I, FIOROGOOD, ELIZABETH, CONSOLAZIO, W V, and LAIBOTT, I H Renal function in patients with gout, Jr Clin Invest, 1940, xix, 525-535
- 133 COPEMAN, W S C Notes on treatment of the rheumatic diseases in the B E F, Jr Roy Army Med Corps, 1940, lxii, 277-285
- 134 COPEMAN, W S C, and BIRT, H A The treatment of muscular rheumatism by injection, Post-Grad Med Jr, 1940, xvi, 293-298
- 135 COLTIER, J S Physical therapy in the military service, Jr Am Med Assoc, 1940, cxv, 804-806
- 136 COLTIER, J S Physical therapy in medical education, Jr Assoc Am Med Coll, 1940, xi, 285-290
- 137 Council on Medical Education and Hospitals Approved schools for physical therapy technicians, Jr Am Med Assoc, 1940, cxiv, 1262-1263
- 138 Council on Medical Education and Hospitals Approved schools of occupational therapy, Jr Am Med Assoc, 1940, cxiv, 1262
- 139 Council on Pharmacy and Chemistry "Sulfathiazole" and "sulfamethylthiazole" the nonproprietary names for 2-sulfanilamidothiazole and 2-sulfanilamido-4-methylthiazole, Jr Am Med Assoc, 1940, cxiv, 2387
- 140 COX, O F, and WATKINS, J H A cooperative plan for the rapid appraisal of the chemotherapy of gonorrhea in the male, Am Jr Syph, Gonorr, and Ven Dis, 1940, xxv, 732-736
- 141 CULP, O S Treatment of gonorrheal arthritis, an analysis of 200 cases, Jr Urol, 1940, xliii, 737-765
- 142 CULP, O S Treatment of gonorrhea with sulfathiazole, Jr Urol, 1940, xliii, 367-376
- 143 CULP, O S, and COBEY, M C Gonorrheal arthritis A proposed plan of sulfanilamide therapy, Jr Bone and Joint Surg, 1940, xxii, 185-199
- 144 CUNNINGHAM, J Occupational therapy, Edinburgh Med Jr, 1940, xlvii, 96-109
- 145 CURTIS, A C, and POLIARD, H M Felty's syndrome, its several features, including tissue changes, compared with other forms of rheumatoid arthritis, ANN INT MED, 1940, xiii, 2265-2284
- 146 DALTON, P P Pelvic infection as the cause of rheumatic and mental disorders, its origin, cause and treatment by electrical methods, especially by diathermy, Brit Jr Rheumat, 1940, ii, 214-228
- 147 DANDURAND, RENE, SCULL, C W, and PEMBERTON, RALPH Observations on reducing substances in the blood plasma of rheumatisants, Jr Lab and Clin Med, 1940, xxv, 348-353
- 148 DANE, P G Menière's disease and gout, Med Jr Australia, 1940, ii, 108
- 149 DAVIDSON, L S P The part played by the voluntary hospitals in the fight against the chronic rheumatic diseases, Jr Roy Inst Pub Health and Hyg, 1940, iii, 245-247
- 150 DAVIS, J B Recurrence of infection after elective operations in cases of healed supuration in bones and joints, Arch Surg, 1940, xli, 1426-1436
- 151 DAVIS, J S, JR Quoted by CECIL, R L¹⁰²
- 152 DAVIS, M W, BRADLEY, W B, BACHERACH, W H, and IVY, A C Effect of Rammstedt operation on incidence of cinchophen ulcer, Proc Soc Exper Biol and Med, 1940, xlv, 66-69
- 153 DAVISON, ROLAND (with the technical assistance of WOOLLEY, MILDRED, and DONOVAN, ELEANOR) The relationship between plasma proteins and erythrocyte sedimentation rates in chronic atrophic arthritis, Jr Lab and Clin Med, 1940, xxv, 935-945
- 154 DAWSON, M H, and HOBBY, GLADYS L The chemotherapy of experimental hemolytic streptococcal infections with gold salts, Jr Pharmacol and Exper Therap, 1940, lxix, 359-364
- 155 DE FOREST, LEE Short wave diathermy, Mil Surgeon, 1940, lxxxvii, 330-336
- 156 DETTRICK, J E The association of congenital hemolytic icterus and gout, Internat Clin, 1940, iii, 264-277

- 157 DE LA CHAPELLE, C E The pathological aspects of rheumatic fever, Bull New York Acad Med, 1940, xvi, 659-669
- 158 DENKER, P G, and KENNEDY, FOSTER Congenital syphilitic syringomyelia with arthropathy of elbow, Jr Am Med Assoc, 1940, cxiv, 408-409
- 159 DICKSON, W E C, and TWORT, R J Thickened ligamenta flava in low back-ache and sciatica, Lancet, 1940, i, 1113-1116
- 160 DIENES, L Origin of L type colonies in bacterial cultures, Proc Soc Exper Biol and Med, 1940, xliii, 703-704
- 161 DIENES, L L type of growth in gonococcus cultures, Proc Soc Exper Biol and Med, 1940, xliiv, 470-471
- 162 DIGIOIA, A M Gonococcus complement fixation test, Jr Lab and Clin Med, 1940, xxvi, 391-393
- 163 DORRANCE, SAMUEL, and MCCLELLAN, W S Effect of natural carbonated baths on rate and amplitude of pulse and blood pressure, Arch Phys Therap, 1940, xxi, 133-139.
- 164 DOWLING, G B Generalized scleroderma, Brit Jr Dermat, 1940, lii, 242-256
- 165 DRISCOLL, R E, and MARKSON, D E One hundred (100) cases of arthritis treated with a comparatively non-toxic gold compound, Illinois Med Jr, 1940, lxxviii, 503-504
- 166 DUNN, C W Present status of endocrine therapy in arthritis, Med Clin North America, 1940, xxiv, 1697-1708
- 167 DUSTIN, C C, and WEYLER, H L C Chronic brucellosis 1 The incidence of chronic undulant fever in Rhode Island, New England Jr Med, 1940, ccxxii, 670-673
- 168 EAGLES, G H, and BRADLEY, W H The agglutination of virus-like particles from rheumatic exudates in acute rheumatic fever, Proc Internat Cong Microbiol, 1939, 371-372
- 169 ECHTMAN, J Therapeutic application of short wave current, Med Rec, 1940, clii, 43, 88
- 170 Editorial The rheumatologist in war time, Brit Jr Rheumat, 1940, ii, 185-188
- 171 EDSTROM, GUNNAR Is spondylarthritis ankylopoietica an independent disease or a rheumatic syndrome? Acta med Scandinav, 1940, civ, 396-413
- 172 EGGERS, HARRY Necroscleritis nodosa associated with chronic rheumatoid polyarthritis, report of case, Arch Ophth, 1940, xliii, 501-506
- 173 ELKINGTON, G W, WILSON, G S, TAYLOR, JOAN, and FULTON, F A mild epidemic of undulant fever in a boys' school due to drinking raw milk, Brit Med Jr, 1940, i, 477-478
- 174 ELKINS, E C A simple device for forced flexion of the knee, Arch Phys Therap, 1940, xxi, 468-469
- 175 ELLMAN, PHILIP, LAWRENCE, J S, and THOROLD, G P Gold therapy in rheumatoid arthritis, Brit Med Jr, 1940, ii, 314-316
- 176 ENGEL, D The permeability of the synovial membrane, Quart Jr Exper Physiol, 1940, xxv, 231-244
- 177 EPSTLIN, B S Comparative study of valvular calcifications in rheumatic and in non-rheumatic heart disease, Arch Int Med, 1940, lxx, 279-290
- 178 EPSTEIN, B S Roentgenologic differentiation of rheumatic from non-rheumatic mitral valve calcifications, Am Jr Roentgenol, 1940, xliiv, 704-708
- 179 EPSTEIN, NATHAN, and McDONALD, F. C Blood-phosphorus studies in rheumatic fever, New England Jr Med, 1940, ccxxii, 943-946
- 180 EPSTEIN, A C, and KINFIL, JACK Pain in the shoulder as a sequel to myocardial infarction, Arch Int Med, 1940, lxxi, 800-806
- 181 EVANS, W A, JR The roentgenological demonstration of the true articular space with particular reference to the knee joint and the internal semilunar cartilage, Am Jr Roentgenol, 1940, xliii, 860-864
- 182 FARQUHAR, L R, and PAUL, J R Rheumatic fever in New Haven, Conn; survey of recent hospital admissions Pub Health Rep, 1940, lv, 1903-1913

- 183 FARLAN, G E, JR, and RAIBURN, F W The blood in arthritis, *Med Clin North America*, 1940, *xiv*, 1633-1645
- 184 FENTON, JAMES The fight against rheumatism, role of local authorities, *Jr Roy Inst Pub Health and Hyg*, 1940, *iii*, 52-56
- 185 FERDERBER, M B Report of the third year of fever therapy research, *Dept Indust Hyg, School of Med, Univ Pittsburgh*, 1940, 21 pp
- 186 FERGUSON, CHARLES, BUCKHOITZ, MAURICE, and HINGSON, R A Sulphapyridine in the treatment of gonococcal infections after sulphanilamide failure, *Am Jr Med Sci*, 1940, *cc*, 365-366
- 187 FERGUSON, E L, and DANGREFFID, L F Wounds penetrating the knee-joint, *Brit Med Jr*, 1940, *i*, 339-340
- 188 FERGUSON, L K, and THOMPSON, W D Internal derangements of the knee joint, an analysis of one hundred cases with follow-up study, *Ann Surg*, 1940, *cxi*, 454-470
- 189 FINDLAY, G M, MACKENZIE, R D, and MACCALLUM, F O Chemotherapeutic experiments on pleuropneumonia-like organisms in rodents, *Brit Jr Exper Path*, 1940, *xvi*, 13-22
- 190 FITCH, W K Nomenclature of modern chemotherapeutical drugs, *Practitioner*, 1940, *cxli*, 5-15
- 191 FLETCHER, ERNEST Chaulmoogra oil in the treatment of chronic arthritis, *Post-Grad Med Jr*, 1940, *xvi*, 299-302
- 192 FLETCHER, G B Underwater or pool treatment of certain conditions of muscles, nerves and joints, *Tri-State Med Jr*, 1940, *xii*, 2411-2413, 2418
- 193 Foreign Letters Gonorrheal arthritis secondary to blood transfusion, *Jr Am Med Assoc*, 1940, *cxv*, 999
- 194 FORESTIER, J, and ROBERT, P X-ray diagnosis in chronic arthritis, *Proc Roy Soc Med*, 1940, *xxxiii*, 707-724
- 195 FOSHAY, LIE The laboratory diagnosis of undulant fever *Am Jr Clin Path*, 1940, *x*, 176-187
- 196 FOX, R F Physical treatment, the case for autonomous clinics, *Lancet*, 1940, *i*, 1175-1176
- 197 FRAZIER, V E Underwater therapy in chronic arthritis, *Jr Missouri Med Assoc*, 1940, *xxxvii*, 192-193
- 198 FREUDENTHAL, W Generalized scleroderma and dermatomyositis A histological comparison, *Brit Jr Dermat*, 1940, *lii*, 289-295
- 199 FREUND, ERNST The pathological significance of intra-articular pressure, *Edinburgh Med Jr*, 1940, *xlvii*, 192-203
- 200 FREYBERG, R H, BLOCK, W D, and FROMER, M F A study of sulfur metabolism and the effect of sulfur administration in chronic arthritis, *Jr Clin Invest*, 1940, *xix*, 423-435
- 201 FREYBERG, R H, BLOCK, W D, and LEVEY, S Metabolism, toxicity and manner of action of gold compounds used in the treatment of arthritis I Human plasma and synovial fluid concentration and urinary excretion of gold during and following treatment with gold sodium thiomalate, gold sodium thiosulfate, and colloidal gold sulfide, *Jr Clin Invest*, 1941, *xx*, 401-412
- 202 FREYBERG, R H, SMYTH, C J, BLOCK, W D, and PRESTON, W S Arthritis, acute gonococcal and gouty, *Jr Michigan Med Soc*, 1940, *xxxix*, 402-407
- 203 FRIEDLANDER, MAE, SILBERT, SAMUEL, and BIERMAN, WILLIAM Regulation of circulation in the skin and muscles of the lower extremities, *Am Jr Med Sci*, 1940, *cxix*, 657-668
- 204 FRIPP, A T The problem of early diagnosis in surgical tuberculosis, *Jr Roy Inst Pub Health and Hyg*, 1940, *iii*, 127-138
- 205 GAULD, R L, and READ, FRANCES E M Studies of rheumatic disease III Familial association and aggregation in rheumatic disease, *Jr Clin Invest*, 1940, *xix*, 393-398

- 206 GAULD, R L, and RLAD, FRANCES E M Studies in rheumatic disease V The age at onset of primary rheumatic attack, Jr Clin Invest, 1940, xix, 729-734
- 207 GECKELER, E O The painful shoulder, Hahnemann Monthly, 1940, lxxv, 463-479
- 208 GELLMAN, MOSES Injury to intervertebral discs during spinal puncture, Jr Bone and Joint Surg, 1940, xxii, 980-985
- 209 GERMAN, J D, and KING, R L The use of gold salts in arthritis, Clin Virginia Mason Hosp, 1940, xix, 1-6
- 210 GEVALT, F C, JR, and LEVINE, S A Significance of Ewart's sign, Internat Clin, 1940, iv, 1-5
- 211 GHORMLEY, R K, BICKEL, W H, and DICKSON, D D A study of acute infectious lesions of the intervertebral disks, South Med Jr, 1940, xxxiii, 347-353
- 212 GIBSON, A Osteo-arthritis of the hip-joint, Manitoba Med Rev, 1940, xx, 113-115
- 213 GIBSON, STANLEY Prognosis in juvenile rheumatic fever, Illinois Med Jr, 1940, lxxviii, 341-344
- 214 GILL, A B The treatment of tuberculosis of the spine, introduction, Jr Bone and Joint Surg, 1940, xxii, 796-798
- 215 GINZLER, A M, and FOX, T T Disseminated lupus erythematosus a cutaneous manifestation of a systemic disease (Libman-Sacks), report of a case, Arch Int Med, 1940, lxxv, 26-50
- 216 GOLDBERG, T S A comparative study of bee venom and salicylates in the treatment of arthritis, Mississippi Valley Med Jr, 1940, lxxii, 190-193
- 217 GOLDFAIN, E Gout (metabolic arthritis), Jr Oklahoma Med Assoc, 1940, xxxiii, 3-5
- 218 GOLDSMITH, M A Rheumatic heart disease in children, Pub Health Nursing, 1940, xxxii, 711-713
- 219 GOLDTHWAIT, J E The rib joints, New England Jr Med, 1940, ccxxxiii, 568-573
- 220 GORDON, J O, and HEACOCK, C H Roentgenologic demonstration of localized gas in caisson disease, Jr Am Med Assoc, 1940, cxiv, 570-571
- 221 GORENBERG, HAROLD, and McGEARY, JOHN Rheumatic heart disease in pregnancy, an evaluation of the history, Jr Med Soc New Jersey, 1940, xxxvii, 114-115
- 222 GOTSHALK, H C, and WAYSON, J T Acute arthritis associated with myocarditis simulating acute lupus erythematosus, report of a case, Arch Dermat and Syph, 1940, xli, 1053-1059
- 223 GRANT, R T Observations on periarteritis nodosa, Clin Sci, 1940, iv, 245-275
- 224 GREEN, C A Reactions induced by intradermal injection of rheumatic joint fluid neutralization by convalescent sera, Proc Roy Soc Med, 1940, xxxiii, 421-424
- 225 GREEN, C A, GLAZEBROOK, A J, THOMSON, S, and HOPKINS, W A Preliminary observations on the use of convalescent serum in the treatment of acute rheumatism, Proc Roy Soc Med, 1940, xxxiii, 275-282
- 226 GREFNF, J A Diagnosis and medical treatment of brucellosis, Jr Iowa Med Soc, 1940, xxx, 252-254
- 227 GRIFFITHS, W J Biochemical aspects of dermatomyositis, Brit Jr Dermat, 1940, lii, 295-304
- 228 GROSS, LOUIS The cardiac lesions in Libman-Sacks disease, with a consideration of its relationship to acute diffuse lupus erythematosus, Am Jr Path, 1940, xvi, 375-408
- 229 GUNZBURG Physical medicine in industry and war, Brit Jr Phys Med, 1940, iii, 168-171
- 230 GUTSTEIN, M Common rheumatism and physiotherapy, Brit Jr Phys Med, 1940, iii, 46-50
- 231 HALL, S L Growth following fusion for tuberculosis of the knee in children, Jr Bone and Joint Surg, 1940, xxii, 1048-1053
- 232 HADLEY, R L Rheumatoid arthritis, etiology and treatment, Arch Phys Therap, 1940, xxi, 671-677
- 233 HALLART, G E The surgical treatment of degenerative arthritis of the knee joint, Jr Bone and Joint Surg, 1940, xxii, 717-729

- 234 HALL, M G, BAYLES, T B, and SOUTTER, PHYLLIS Vitamin A requirements in rheumatoid arthritis, *New England Jr Med*, 1940, ccxxiii, 92-96
- 235 HAMBY, W B The interlaminal removal of protrusions of the intervertebral disc at the fourth and fifth lumbar interspaces, *Surg, Gynec, and Obst*, 1940, lxxxi, 344-346
- 236 HAMILTON, J F The use and misuse of physical therapeutics in the treatment of chronic arthritis, *Memphis Med Jr*, 1940, xv, 184-187
- 237 HAMILTON, J R The rheumatic problem, *Virginia Med Monthly*, 1940, lxxvii, 357-360
- 238 HAMPTON, A O Iodized oil myelography, use in the diagnosis of rupture of the intervertebral disk into the spinal canal, *Arch Surg*, 1940, xl, 444-453
- 239 HARR, H F The diagnosis of Marie-Strumpell arthritis with certain aspects of treatment, *New England Jr Med*, 1940, ccxxiii, 702-705
- 240 HARE, H F, and KIMMEL, C B Treatment of atrophic spondylitis with radiation therapy preliminary report, *Lahey Clin Bull*, 1940, i, 22-26
- 241 HARKNFSS, A H Chemotherapy of gonorrhea and its complications with special reference to the cause and prevention of failures, *Brit Jr Ven Dis*, 1940, xvi, 211-231
- 242 HARMAN, J B, and YOUNG, R H Muscle lesions simulating visceral disease, *Lancet*, 1940, i, 1111-1113
- 243 HARRIS, H J Physical therapy of various manifestations of brucellosis (undulant fever), *Arch Phys Therap*, 1940, xxi, 605-611
- 244 HARRIS, R I, and COULTHARD, H S End results of treatment of Pott's disease, *Jr Bone and Joint Surg*, 1940, xxii, 862-874
- 245 HARTSOCK, C L Headache from arthritis of the cervical spine, *Med Clin North America*, 1940, xxiv, 329-333
- 246 HAZEL, O G, and HULL, W M Dermatomyositis in children, a report of two cases with a fatal termination, *South Med Jr*, 1940, xxxiii, 809-818
- 247 HEDLEY, O F Rheumatic heart disease in Philadelphia hospitals, a study of 4,653 cases of rheumatic heart disease, rheumatic fever, Sydenham's chorea, and subacute bacterial endocarditis, involving 5,921 admissions to Philadelphia hospitals from January 1, 1930, to December 31, 1934, *Pub Health Rep*, 1940, iv, 1599-1619
- 248 HEDLEY, O F Rheumatic heart disease in Philadelphia hospitals, a study of 4,653 cases of rheumatic heart disease, rheumatic fever, Sydenham's chorea and subacute bacterial endocarditis, involving 5,921 admissions to Philadelphia hospitals from January 1, 1930, to December 31, 1934 II Age, race and sex distribution and interrelation of rheumatic fever, Sydenham's chorea, rheumatic heart disease, and subacute bacterial endocarditis, *Pub Health Rep*, 1940, iv, 1647-1691
- 249 HEDLEY, O F Rheumatic heart disease in Philadelphia hospitals, a study of 4,653 cases of rheumatic heart disease, rheumatic fever, Sydenham's chorea and subacute bacterial endocarditis, involving 5,921 admissions to Philadelphia hospitals from January 1, 1930, to December 31, 1934 III Fatal rheumatic heart disease and subacute bacterial endocarditis, *Pub Health Rep*, 1940, iv, 1707-1740
- 250 HEDLEY, O F Rheumatic heart disease in Philadelphia hospitals, a study of 4,653 cases of rheumatic heart disease, rheumatic fever, Sydenham's chorea, and subacute bacterial endocarditis, involving 5,921 admissions to Philadelphia hospitals from January 1, 1930, to December 31, 1934 IV Influence of season and certain meteorological conditions, *Pub Health Rep*, 1940, iv, 1809-1831
- 251 HEDLEY, O F Rheumatic heart disease in Philadelphia hospitals, a study of 4,653 cases of rheumatic heart disease, rheumatic fever, Sydenham's chorea and subacute bacterial endocarditis involving 5,921 admissions to Philadelphia hospitals from January 1, 1930, to December 31, 1934 V Distribution by locality of rheumatic conditions in Philadelphia, *Pub Health Rep*, 1940, iv, 1845-1862
- 252 HEDLEY, O F Rheumatic heart disease in Philadelphia hospitals, a study of 4,653 cases of rheumatic heart disease, rheumatic fever, Sydenham's chorea, and subacute bacterial endocarditis involving 5,921 admissions to Philadelphia hospitals from Janu-

- ary 1, 1930, to December 31, 1934, Pub Health Rep, 1941, Washington, D C, U S Government Printing Office, Reprint No 2195, pp 1-138
- 253 HEILMAN, F R Chemotherapy in experimental infections caused by *Streptobacillus moniliformis*, Science, 1940, xci, 366-367.
- 254 HELFET, A J New conception of parathyroid function and its clinical application, preliminary report on results of treatment of generalized fibrocystic and allied bone diseases and of rheumatoid arthritis by aluminum acetate, Brit Jr Surg, 1940, xxvii, 651-677
- 255 HENCH, P S Recent investigations on rheumatism and arthritis in the United States, Ann Rheumat Dis, 1940, ii, 19-40
- 256 HENCH, P S The advantages of hepatic injury and jaundice in certain conditions, notably the rheumatic diseases, Med Clin North America, 1940, xxiv, 1209-1237
- 257 HENCH, P S An oft recurring disease of joints (arthritis, peri-arthritis, para-arthritis) apparently producing no articular residues, Jr Am Med Assoc, 1940, cxv, 2207
- 258 HENCH, P S Chronic arthritis, chronic infectious arthritis, chronic senescent arthritis, gout In Modern medical therapy in general practice, 1940, The Williams & Wilkins Company, Baltimore, pp 3298-3397
- 259 HENCH, P S Gout and gouty arthritis In Cecil's textbook of medicine, Ed 5, 1940, W B Saunders Company, Philadelphia, pp 658-672
- 260 HENDERSON, M S Some mechanical derangements of the knee and shoulder, Am Jr Surg, 1940, xlviii, 535-543.
- 261 HENDERSON, M S, and POLLOCK, G A Surgical treatment of osteoarthritis of the hip joint, Jr Bone and Joint Surg, 1940, xxii, 923-931
- 262 HENSON, E B The use of oxygen in joints in preventing adhesions from trauma and infection, South Med Jr, 1940, xxxiii, 776-778
- 263 HEYMANN, WALTER, and ENRIGHT, LFNA S Artificial fever treatment in infants and children, methods, indications and results, Ohio State Med Jr, 1940, xxxvi, 40-43
- 264 HIGHTOWER, L P Undulant fever, Texas State Jr Med, 1940, xxxvi, 542-546
- 265 HILL, L C Observations on the treatment of rheumatoid arthritis, Brit Jr Rheumat, 1940, ii, 202-207
- 266 HILLS, G M The metabolism of articular cartilage, Biochem Jr, 1940, xxxiv, 1070-1077
- 267 HINDLEY-SMITH, J D Remedial treatment in war time and after, Brit Jr Phys Med, 1940, iii, 2-5
- 268 HINDLEY-SMITH, J D The treatment of chronic rheumatism by vaccine therapy, Brit Jr Rheumat, 1940, ii, 228-236
- 269 History Occup Therap, 1940, xix, 27-34
- 270 HITCHCOCK, H H Spondylolisthesis, observations on its development, progression, and genesis, Jr Bone and Joint Surg, 1940, xxii, 1-16
- 271 HOBSON, J J Acute rheumatic fever, Jr Tennessee Med Assoc, 1940, xxxiii, 60-65
- 272 HOFFMAN, C A Clinical observations in the treatment of gonorrhea with sulfapyridine, West Virginia Med Jr, 1940, xxxvi, 347-352
- 273 HOFFMAN, H L Rheumatic heart disease in the navy some observations on diagnosis and treatment, Jr Roy Nav Med Serv, 1940, xxvi, 226-238
- 274 HOLL, F J, SIMON, A J, and HECTOR, L G The effect of short electric wave radiation on the development of *Trichinella spiralis*, Am Jr Hyg, 1940, xxi, 32-36
- 275 HOLLAND, C F. Undulant fever, outbreak at Michigan State College, Jr Michigan Med Soc, 1940, xxxix, 666-670
- 276 HOLLANDER, E Treatment of chorea by injection of ether extract of brain lipoids, Med Rec, 1940, clii, 300-301
- 277 HOFFENBURG, W R Incidence of rheumatism in relation to pigmentation of hair and eyes, Med Officer, 1940, lxiii, 77
- 278 HORDIE Third annual report of the Empire Rheumatism Council, Ann Rheum Dis, 1940, ii, 67-73

- 279 HORDFR Fourth annual report of the Empire Rheumatism Council, *Ann Rheum Dis*, 1940, *ii*, 159-165
- 280 HORDFR Rheumatism, notes on its causes, its incidence and its prevention, with a plan for national action, H K Lewis & Co, Ltd, London, pp 5-60
- 281 HORVITZ, R S Notes on the history of rheumatism and gout, *New England Jr Med*, 1940, *ccxliii*, 754-760
- 282 HORN, W S Chronic brucellosis as a major cause of neurasthenia, *Jr Kansas Med Soc*, 1939, *xl*, 498-504
- 283 HORN, W S Sulfamidamide in the treatment of undulant fever, *Texas State Jr Med*, 1940 *xxxvi*, 232-237
- 284 HORWITZ, THOMAS Degenerative lesions in the cervical portion of the spine, *Arch Int Med*, 1940, *lcv*, 1178-1191
- 285 HOSKINS, W H Osteoarthritis, *Jr Florida Med Assoc*, 1940, *xxvi*, 496-498
- 286 HOWARD, M C Rheumatic heart disease, *Nebraska Med Jr*, 1940, *xxv*, 51-55
- 287 HUDDLESON, I F, and MUNGER, MARYLE A study of an epidemic of brucellosis due to *Brucella melitensis*, *Am Jr Pub Health*, 1940, *xxx*, 944-954
- 288 HUDDLESON, I F, and PENNELL, R B The preparation and purification of *Brucella* antiserum, *Science*, 1939, *xc*, 571-572
- 289 HUDDLESTON, O L Relationship of physical therapy to the practice of medicine, *Rocky Mountain Med Jr*, 1940, *xxvii*, 513-517
- 290 HUGHES, LAURENCE Acute rheumatism, *Med Jr Australia*, 1940, *ii*, 423-427
- 291 HUNT, G C The treatment of gonorrhea with a new sulfamidamide derivative, *Illinois Med Jr*, 1940, *lxxviii*, 183-186
- 292 HURST, J H Actinomycosis progressively involving the retina, lungs, and vertebrae, *Med Bull Vet Admin*, 1940, *xvii*, 90-92
- 293 INSTONE, STELLA Pneumococcal arthritis complicating lobar pneumonia treated with sulphapyridine, recovery, *Brit Med Jr*, 1940, *ii*, 523
- 294 ISHMAEL, W K Autohemotherapy combined with artificial fever, further observations in the treatment of rheumatic disease, *Arch Phys Therap*, 1940, *xxi*, 335-339
- 295 JACQUES, R H Relation between reduced ascorbic-acid levels of the blood plasma and rheumatoid arthritis, *Jr Bone and Joint Surg*, 1940, *xxii*, 324-326
- 296 JOHNSON, H F Herniation of the intervertebral disc with referred sciatic symptoms, a study of forty cases, *Jr Bone and Joint Surg*, 1940, *xxii*, 708-716
- 297 JOHNSTONE, R T The industrial back from the internist's viewpoint, *Am Jr Surg*, 1940, *xlvi*, 544-547
- 298 JONES, G M, JR A summary of the signs and symptoms of periarteritis nodosa, observations in fourteen pathologically proven cases seen at the University Hospital, *Univ Hosp Bull*, Ann Arbor, 1940, *vi*, 91-92
- 299 JONES, T D Etiology of rheumatic fever, discussion, *Jr Pediat*, 1939, *xv*, 772-785
- 300 JONES, T D, and MOTE, J R The clinical importance of infection of the respiratory tract in rheumatic fever, *Jr Am Med Assoc*, 1939, *cxiii*, 898-902
- 301 JOSTES, F A Backache, a manipulative treatment without anaesthesia, *Mississippi Valley Med Jr*, 1940, *lxii*, 114-118
- 302 JOSTES, F A Low back lesions differential diagnostic problems, *Surg Clin North America*, 1940, *xx*, 1413-1437
- 303 KAISER, A D Dietary factors in rheumatic disease of childhood, *Jr Am Dietet Assoc*, 1940, *xvi*, 787-791
- 304 KAISER, HELEN Occupational therapy in a general hospital with orthopedic cases from the physical therapy point of view, *Occup Therap*, 1940, *xix*, 1-8
- 305 KAPLAN, LOUIS Painful shoulder, diagnosis and treatment, *Pennsylvania Med Jr*, 1940, *xliv*, 289-297
- 306 KARSNER, H T, and KOLETSKY, SIMON Calcific sclerosis of the aortic valve, *Trans Assoc Am Phys*, 1940, *lv*, 188-195

307. KEEGAN, J J, and FINLAYSON, A I · Low back and sciatic pain caused by intervertebral disc herniation, *Nebraska Med Jr*, 1940, xxv, 179-184
308. KEIL, HARRY Dermatomyositis and systemic lupus erythematosus I A clinical report of "transitional" cases, with a consideration of lead as a possible etiologic factor, *Arch Int Med*, 1940, lxvi, 109-139
309. KEIL, HARRY Dermatomyositis and systemic lupus erythematosus II A comparative study of the essential clinicopathologic features, *Arch Int Med*, 1940, lxvi, 339-383
310. KEITH, N M The renal problem in lupus erythematosus, *Proc. Staff Meet. Mayo Clin*, 1940, xv, 682-683
311. KELCHNER, C H Fibrositis, *Med Clin North America*, 1940, xxiv, 1647-1657
312. KELIKIAN, H The pathological physiology of joints, *Surg, Gynec, and Obst*, 1940, lxxi, 416-436
313. KELLER, A E A comparison of skin reactions obtained by the use of *Brucella* nucleoprotein (brucellergen) and of heated *Brucella* organisms in sensitized individuals, *South Med Jr*, 1940, xxxiii, 1180-1184
314. KELLGREN, J H Some painful joint conditions and their relation to osteoarthritis, *Clin Sci*, 1939, iv, 193-205
315. KELLY, L C Colitis following injection of gold salts, *New York State Jr Med*, 1940, xl, 1192-1194
316. KENDRICK, J I *Staphylococcus* septicemia with septic arthritis of the knee treated with sulfapyridine, report of a case, *Cleveland Clin Quart*, 1940, vii, 35-36
317. KENDRICK, J I Physical therapy principles of peri-arthritis of the shoulder, *Arch Phys Therap*, 1940, xxi, 41-44
318. KENDRICK, J I Treatment of peri-arthritis of shoulder, *Med Clin North America*, 1940, xxiv, 525-532
319. KENT, J P Acute suppurative arthritis, a simple method for treatment, *Indust Med*, 1940, ix, 368-370
320. KEY, J A Foreign body arthritis, *Surg, Gynec, and Obst*, 1940, lxx, 897-902
321. KEY, J A The pathology of tuberculosis of the spine, *Jr Bone and Joint Surg*, 1940, xxii, 799-806
322. KEY, J A, FRANKEL, C J, and BURFORD, T H The local use of sulfamidamide in various tissues, *Jr Bone and Joint Surg*, 1940, xxii, 952-958
323. KIERLAND, R R Classification and cutaneous manifestations of lupus erythematosus, *Proc. Staff Meet Mayo Clin*, 1940, xi, 675-677
324. KINELL, JACK, and HADEN, R L Gout a review of 62 cases, *Med Clin North America*, 1940, xxiv, 429-441
325. KING, DON, and RICHARDS, VICTOR Osteochondritis dissecans of the hip, *Jr Bone and Joint Surg*, 1940, xxii, 327-348
326. KING, E S J The formation of ganglia and cysts of the menisci of the knee, observations on the Golgi apparatus, *Surg, Gynec, and Obst*, 1940, lxx, 150-156
327. KINNEY, T D, and MAHER, MARY M Dermatomyositis, a study of five cases, *Am Jr Path*, 1940, xvi, 561-594
328. KLEIN, R I, LEVINSON, S A, and ROSENBLOOM, PHILIP Weltmann reaction and sedimentation rate during rheumatic fever of childhood, *Am Jr Dis Child*, 1940, lxx, 48-66
329. KRIEGERBERGER, EMMA The pleuropneumonia-like organisms further comparative studies and a descriptive account of recently discovered types, *Jr Hyg*, 1940, xl, 204-222
330. KLING, D H Histamine cataphoresis in rheumatic conditions and in disturbances of the peripheral circulation, *Med Rec*, 1940, cli, 388-391
331. KLUFFEL, H C Hyperuricemia and inflammations of the eye, *Am Jr Ophth*, 1940, xxiii, 867-872
332. KOLVER, J A (with the assistance of ANNA M RULE) The therapeutic activity of sulfanilamide and allied compounds in experimental brucellosis of mice, *Jr Pharmacol and Therap*, 1940, lxviii, 406-412

- 333 KOVACS, RICHARD Evaluation of short-wave diathermy, *Brit Jr Phys Med*, 1940, *iii*, 5-10
- 334 KOVACS, RICHARD Physical therapy in general practice, *Jr Med Soc New Jersey*, 1940, *xxvii*, 458-461
- 335 KOVACS, RICHARD Recent progress in physical therapy, *Med Rec*, 1940, *cli*, 261-263
- 336 KRUSEN, F H *Physical therapy in relation to orthopedic surgery with particular reference to the influence of Sir Robert Jones on this relationship*, *West Jr Surg*, 1939, *xlii*, 646-653
- 337 KRUSEN, F H Physical treatment of arthritis, *Arch Phys Therap*, 1940, *xxi*, 144-153
- 338 KRUSEN, F H Backache, the relation of physical therapy to its management, *Canad Med Assoc Jr*, 1940, *xlii*, 534-541
- 339 KRUSEN, F H Physical therapy in arthritis, with special reference to home treatment, *Jr Am Med Assoc*, 1940, *cxv*, 605-615
- 340 KRUSEN, F H Short-wave diathermy, *Mil Surgeon*, 1940, *lxxxvii*, 158-163
- 341 KRUSEN, F H Light therapy, *Modern medical therapy in general practice*, 1940, The Williams & Wilkins Company, Baltimore, pp 528-547
- 342 KRUSEN, F H, and BASOM, W C Certain common types of low backache, conservative management with special reference to physical therapy, *Med Clin North America*, 1940, *xxiv*, 1191-1207
- 343 KUGEL, I H A new local treatment for psoriasis, with report of twenty-one cases, *Med Rec*, 1940, *cli*, 397-401
- 344 KUHN, J G, and FELDMAN, THEODORE The relationship of syphilis to chronic arthritis, *Urol and Cutan Rev*, 1940, *xlv*, 532-535
- 345 KULLBERG, R W, and LOWELL, L M Treatment of arthritis, a physiological approach, *Rocky Mountain Med Jr*, 1940, *xxxvii*, 114-116
- 346 KUSKIN, LAWRENCE, and BROCKMAN, LOUIS The two-step test as diagnostic aid in subclinical rheumatic heart disease, preliminary report, *Arch Pediat*, 1940, *lvii*, 578-584
- 347 KUTTNER, ANN G The effect of large doses of vitamins A, B, C and D on the incidence of upper respiratory infections in a group of rheumatic children, *Jr Clin Invest*, 1940, *xix*, 809-812
- 348 KUTUMBAH, P A study of the lesions in rheumatic heart disease in South India, *Indian Jr Med Research*, 1940, *xxvii*, 631-641
- 349 LAMBIE, C G Study of juvenile gout in patient suffering from chronic erythronoclastic anemia of obscure origin, together with observations upon physical state of uric acid in blood and effects of splenectomy, *Med Jr Australia*, 1940, *i*, 535-558
- 350 LANG, S J The diagnosis of backache, *Illinois Med Jr*, 1940, *lxxvii*, 32-35
- 351 LATHROP, F W Undulant fever, *Jr Med Soc New Jersey*, 1940, *xxxvii*, 466-469
- 352 LAWSON, G B, and GRAYBEAL, A B Hemophilia treated by venesection, *Jr Am Med Assoc*, 1940, *cxiv*, 2299-2300
- 353 LEADER, S A Charcot's arthropathy of both ankles case report, *Am Jr Roentgenol*, 1940, *xliii*, 509-513
- 354 LEAVITT, D G Treatment of suppurative arthritis, *Northwest Med*, 1940, *xxix*, 169-171
- 355 LEBOWITZ, J, and HUNT, H D The diagnostic significance of eosinophilia in periarteritis nodosa, *Am Jr Clin Path*, 1940, *x*, 642-651
- 356 LERNER, CHARLES Hereditary influences in psoriasis, *Jr Invest Dermat*, 1940, *iii*, 347-356
- 357 LEVITT, ABEL, and JASKIEWICZ, S J Rheumatic heart disease, an analysis of 110 cases, *Am Jr Clin Path*, 1940, *x*, 467-471
- 358 LEWIS, R W Roentgen recognition of synovium, *Am Jr Roentgenol*, 1940, *xliv*, 170-174
- 359 LEWIS, T Notes on scleroderma (dermatomyositis), *Brit Jr Dermat*, 1940, *lii*, 233-242

- 360 LIEBMAN, C, and ISEMAN, R M Osteochondritis dissecans, *Am Jr Roentgenol*, 1940, xliii, 865-870
- 361 LINCOLN, MIRIAM Undulant fever, successful treatment with vaccine and neoprontosil, *Northwest Med*, 1940, xxxix, 64-65
- 362 LIPKIN, EZRA Observations on the treatment of rheumatic conditions with local injection of procaine solution, preliminary report, *North End Clin Quart*, 1940, 1, 8-13
- 363 LITTLE, NORMAN Traumatic backache, *Med Jr Australia*, 1939, ii, 755-758
- 364 LLOYD, V E, and ERSKINE, D Sulphathiazole and sulphamethylthiazole in gonorrhoea, *Lancet*, 1940, ii, 186-187
- 365 LOCKE, ARTHUR, and COHEN, M A Effect of inhaled carbon dioxide in rheumatoid (atrophic) arthritis, *Proc Soc Exper Biol and Med*, 1940, xliii, 611-615
- 366 LOEWE, LEO, and LENKE, S E Cardiac lesions resembling Aschoff bodies in rabbits, *Jr Exper Med*, 1940, lxxi, 89-94
- 367 LONG, P H, HAVILAND, J W, and EDWARDS, LYDIA B Acute toxicity, absorption and excretion of sulfathiazole and certain of its derivatives, *Proc Soc Exper Biol and Med*, 1940, xliii, 328-332
- 368 LONG, P H, HAVILAND, J W, EDWARDS, LYDIA B, and BLISS, ELEANOR A The toxic manifestations of sulfanilamide and its derivatives, with reference to their importance in the course of therapy, *Jr Am Med Assoc*, 1940, cxv, 364-368
- 369 LOVE, J G Treatment of protruded intervertebral disks, *Minnesota Med*, 1940, xxiii, 692-695
- 370 LOVE, J G Removal of protruded intervertebral disks without laminectomy, *Proc Staff Meet Mayo Clin*, 1939, xiv, 800
- 371 LOVE, J G, and WALSH, M N Intraspinal protrusion of intervertebral disks, *Arch Surg*, 1940, xl, 454-484
- 372 LUTWAK-MANN, CECILIA Enzyme systems in articular cartilage, *Biochem Jr*, 1940, xxxiv, 517-527
- 373 LUX, A Spondylarthritis due to posture and its treatment, *Am Jr Surg*, 1940, xlviii, 654-657
- 374 MACBRIDE, C M Toxic hepatitis and acute yellow atrophy, following medication with a cinchophen-containing "cold cure," *Jr Am Med Assoc*, 1940, cxiv, 316-318
- 375 MACDONALD, LAURENCE Paraarticular calcification of the shoulder a survey, *Med Jr Australia*, 1940, ii, 467-469
- 376 MACKEE, G M, and ASTRACHAN, G D The value of liver extract in cases intolerant to arsenicals, heavy metals, and radiation, *Jr Invest Dermat*, 1940, iii, 409-442
- 377 MACKINNON, D J Recent advances in treatment of gonorrhoea, *Brit Med Jr*, 1940, ii, 448-449
- 378 MACLAIN, C C A case report on the treatment of atrophic arthritis with bee venom, *Mississippi Valley Med Jr*, 1940, lxii, 193-194
- 379 MADSEN, J F Treatment of psoriasis, *Jr Am Med Assoc*, 1940, cxv, 588-590
- 380 MAHONEY, J F, WOLCOTT, R R, and VAN SICKLE, C J Sulfamethylthiazole and sulfathiazole therapy of gonococcal infections, *Am Jr Syph, Gonorr, and Ven Dis*, 1940, xxiv, 613-621
- 381 MANN, A I Present-day treatment of gonorrhea with fever therapy, *Am Jr Syph, Gonorr, and Ven Dis*, 1940, xxiv, 743-744
- 382 MARGOLIS, H M, and EISENSTEIN, V W Some specific measures in the treatment of rheumatoid arthritis, *Jr Am Med Assoc*, 1940, cxv, 1429-1433
- 383 MARQUIS, D W Treatment of acute rheumatic fever, *Trans Am Therap Soc*, 1940, xl, 124-127
- 384 MARSHALL, F K Jr The present status and problems of bacterial chemotherapy, *Surgery*, 1940, xci, 345-350
- 385 MARTIN, A I Clinical aspects of rheumatic fever in children, *Bull New York Acad Med*, 1940, 2, xvi, 475-482

- 386 MARTIN, C P The movements of the shoulder-joint, with special reference to rupture of the supraspinatus tendon, *Am Jr Anat*, 1940, lxi, 213-234
- 387 MARTUCCI, A A Physical therapy in the treatment of chronic arthritis, *Med Clin North America*, 1940, xlii, 1685-1696
- 388 MATTHEWS, M W The diagnosis of gout, *New Orleans Med and Surg Jr*, 1940, xii, 624-630
- 389 MAYNED, G R The incidence of the four main blood groups in rheumatic heart disease, *Arch Dis Childhood*, 1940, xv, 181-183
- 390 MAYER, LEO A critical study of tuberculosis of the spine in children, *Jr Bone and Joint Surg*, 1940, xii, 875-877
- 391 McCAULEY, J C Operative treatment of neurotrophic joints, *Urol and Cutan Rev*, 1940, xli, 592-594
- 392 McCLELLAN, W S Hydrotherapy and balneotherapy In *Modern medical therapy in general practice*, 1940, The Williams & Wilkins Company, Baltimore, pp 415-445
- 393 McCULLOCH, HUGH Rheumatic fever diagnosis and treatment, *Jr Michigan Med Soc*, 1940, xxxiv, 243-248
- 394 McCURDY, G A Affections of the synovial membrane, *Bull Vancouver Med Assoc*, 1940, xli, 334-338
- 395 McEWEN, CURRIER Rheumatic heart disease In *STROUD, W D Diagnosis and treatment of cardiovascular disease*, 1940, F A Davis Company, Philadelphia, vol 1, chap iii, pp 42-83
- 396 McEWEN, CURRIER Diseases of doubtful or unknown etiology, rheumatic fever In *Modern medical therapy in general practice*, 1940, The Williams & Wilkins Company, Baltimore, 1984-2004
- 397 MCGAVACK, T H Some recent advances in the treatment of hemophilia, *Med Clin North America*, 1940, xlii, 791-805
- 398 MCGREGOR, H G The psychological factor in rheumatic disease, *Practitioner*, 1939, cxliii, 627-636
- 399 McKENNA, D E Discussion, *New York State Jr Med*, 1936, xxxvi, 1530-1531
- 400 McKENNA, D E Tendinitis of the shoulder, *Med Times, New York*, 1940, lxxviii, 259-268
- 401 Medical preparedness Physical standards under selective service, *Jr Am Med Assoc*, 1940, cxv, 1552-1560
- 402 MEIKS, L T The influence of tonsillectomy on the progress of rheumatic heart disease, *Jr Indiana Med Assoc*, 1940, xxxiii, 666-670
- 403 MENGERT, W F Backache as seen by a gynecologist, *Jr Iowa Med Soc*, 1940, xxx, 480-482
- 404 MENNELL, JAMES The prescription of massage and what this implies, *Rheumatism*, 1940, ii, 53-69
- 405 MENTON, J Brucellosis in the midlands of England, *Med Officer*, 1940, Jan 27
- 406 MEYERDING, H W Tuberculosis of the spine treatment and results, *Jr Bone and Joint Surg*, 1940, xxii, 840-850
- 407 MEYERDING, H W, BAKER, G S, LOVE, J G, and CAMERON, D M Spondylolisthesis with protrusion of intervertebral disk and hypertrophied ligamentum flavum associated with multiple loose bodies (osteochondromatosis) of right shoulder joint report of a case, *Proc Staff Meet Mayo Clin*, 1939, xiv, 801-806
- 408 MEYERDING, H W, and POLLOCK, G A Backache common causes and treatment with special reference to physical therapy, *Arch Phys Therap*, 1940, xxi, 69-77
- 409 MEYERDING, H W, and POLLOCK, G A Modern conceptions of backache, *Journal-Lancet*, 1940, i, 225-231
- 410 MILGRAM, J E Tabetic arthropathy, *Urol and Cutan Rev*, 1940, xlii, 653-656
- 411 MILHORAT, ADE T Recent advances in the therapy of diseases of muscle, *Med Clin North America*, 1940, xlii, 769-775

- 412 MILTNER, L J . Technic of examination of the spine and manipulative treatment, Jr Iowa Med Soc , 1940, xxx, 193-196
- 413 MIXTER, W J, and BARR, J S Protrusion of the lower lumbar intervertebral disks, New England Jr Med , 1940, ccxxiii, 523-529
- 414 MOFFETT, MARY Chemotherapy of gonococcal infections in women and children, Brit. Med Jr , 1940, ii, 8-10
- 415 MONTGOMERY, B E The use of bee venom in the treatment of neuritis and arthritis, Illinois' Med Jr , 1940, lxxviii, 148-151
- 416 MONTGOMERY, HAMILTON Pathology of lupus erythematosus, Proc Staff Meet Mayo Clin , 1940, xv, 678-680
- 417 MORALES-OTERO, P, and PONALES-LEBRON, A Effects of sulfanilamide and sulfamethylthiazol on experimental *Brucella (var melitensis)* infection in mice, Proc Soc. Exper Biol and Med , 1940, xlv, 512-515
- 418 MORRISON, R J G Two cases of undulant fever treated with sulfanilamide, Jr Roy Army Med Corps, 1940, lxxv, 45-47
- 419 MUETHER, R O Use of vitamins in chronic arthritis, Jr Missouri Med Assoc , 1940, xxxvii, 111-114
- 420 MUETHER, R O The use of histamine in rheumatoid arthritis, ANN INT MED , 1940, xiii, 2147-2153
- 421 MURRAY, J E, and TYARS, M E A case of Ehlers-Danlos disease, Brit Med Jr , 1940, i, 974
- 422 NATHANSON, LOUIS Pulmonary apical tumefaction simulating bursitis, necessity for routine chest examination in patients with shoulder pain, New York State Jr Med , 1940, xl, 860-864
- 423 NELSON, L A Hyoid bursitis, Texas State Jr Med , 1940, xxxvi, 435-438
- 424 NESBIT, R M Observations upon the site of action of sulfapyridine in gonorrhea, Jr Urol , 1940, xlv, 242-243
- 425 NEUWEIT, FRANK, and NECHELES, H Experimental cinchophen ulcer, Proc Soc Exper Biol and Med , 1940, xlv, 78-81
- 426 O'BRIEN, W A Physical therapy and graduate teaching at University of Minnesota, Arch Phys Therap , 1940, xxi, 180-181
- 427 O'BRIEN, W A Continuation study in physical therapy technology, Physiotherapy Rev , 1940, xx, 145-148
- 428 OCHSNER, H C, and MUMFORD, E B Roentgen therapy for painful conditions of the bones and joints, Radiology, 1940, xxxiv, 444-448
- 429 O'DONOGHUE, A F Backache from an orthopedic standpoint, Jr Iowa Med Soc , 1940, xxx, 476-480
- 430 O'LEARY, P A Prognosis and treatment of lupus erythematosus, Proc Staff Meet Mayo Clin , 1940, xv, 686-688
- 431 O'LEARY, P A, and WAISMAN, MORRIS Dermatomyositis, a study of forty cases, Arch Dermat and Syph 1940, xli, 1001-1019
- 432 OPPENHEIMER, ALBERT Discogenetic disease, Am Jr Surg , 1940, xlvii, 642-650
- 433 OPPENHEIMER, ALBERT The apophyseal intervertebral joints, Surgery, 1940, viii, 699-712
- 434 OPSAHN, ROYD Hematopoiesis and endogenous uric acid, Acta med Scandinav , 1939, cii, 611-628
- 435 OSTOON, R B The medical and social approaches to the problem of chronic rheumatism, Am Jr Med Sci , 1940, cc 429-445
- 436 OXER, G M Amyloidosis complicating rheumatoid arthritis, Med Jr Australia, 1940, i, 233-234
- 437 PAGE, R C, RUSSITT, H. K, and ROSENTHAL, R L Effect of oxalic acid intravenously on blood-coagulation time in three hemophiliacs, ANN INT MED , 1940, xiv, 78-80

- 438 PARRISH, P P, CONSOLF, W A, and BATTAGLIA, JOSEPH Gonococcic arthritis of the newborn treated with sulfanilamide, *Jr Am Med Assoc*, 1940, cxiv, 241-242
- 439 PATTEF, GIADIS Prescribed exercise to be carried out at home, home occupational therapy, *Occup Therap*, 1940, xix, 169-175
- 440 PATTERSON, R L, JR, and PATTERSON, R H Further observations on the treatment of bursitis of the shoulder, *Am Jr Surg*, 1940, xlix, 403-408
- 441 PAULI, J R The epidemiology of rheumatic fever In *STROUD, W D The diagnosis and treatment of cardiovascular disease*, 1940, F A Davis Company, Philadelphia, vol 1, chap 15
- 442 PAULI, J R Environmental factors in rheumatic fever, *Trans Assoc Am Phys*, 1940, lv, 290-293
- 443 PAVEY-SMITH, A B Tonsillectomy and rheumatism, *Med Press*, 1940, cciii, 414-416
- 444 PEERS, R S Gall-bladder its relation to chronic arthritis of uncertain etiology, *California and West Med*, 1939, li, 374-376
- 445 PELOUZE, P S Oral and medical treatment of gonorrhea in the male, *Jr Am Med Assoc*, 1940, cxiv, 1878-1881
- 446 PELOUZE, P S, AND OTHERS Gonorrhea in the male, results of treatment with sulfanilamide, *Jr Am Med Assoc*, 1940, cxv, 1630-1633
- 447 PEMBERTON, RALPH Integration and coordination of therapy in the care of arthritics, *Med Clin North America*, 1940, xxiv, 1767-1777
- 448 PEMBERTON, RALPH, and SCULL, C W Introduction to the problem of rheumatoid disease classification, etiology and diagnosis, *Med Clin North America*, 1940, xxiv, 1591-1601
- 449 PENNABACKER, JOE Sciatica and the intervertebral disc, *Lancet*, 1940, i, 771-777
- 450 PERRY, C B Rheumatic heart disease in identical twins, *Arch Dis Childhood*, 1940, xv, 177-180
- 451 PERRY, C B Streptococcal antifibrinolysin in rheumatoid arthritis and spondylitis ankylopoietica, *Ann Rheumat Dis*, 1940, ii, 147-149
- 452 PFEIFFER, D B, and BACH, T F Reconstructive surgery in chronic rheumatoid arthritics, *Med Clin North America*, 1940, xxiv, 1745-1753
- 453 PHEMISTER, D B Changes in bones and joints resulting from interruption of circulation I General considerations and changes resulting from injuries, *Arch Surg*, 1940, xli, 436-472
- 454 PHILLIPS, R T Chronic arthritis, therapeutic consideration, *Jr Maine Med Assoc*, 1940, xxxi, 95-98
- 455 PIEWES, L W Osteo-arthritis of the hip, *Brit Jr Surg*, 1940, xxvii, 682-695
- 456 PREBLL, E E Gonorrhoea and the sulphonamides, *Med Press*, 1940, cciv, 189-191
- 457 PRESTON, R L The immediate restoration of active extension of the knee following flexion deformities, *Am Jr Surg*, 1940, i, 303-305
- 458 PULCHERIA, SISTER MARY Occupational therapy and orthopedic nursing, *Hosp Progress*, 1940, xxi, 94-97
- 459 PULLINGER, E J Brucellosis, *South African Med Jr*, 1939, xiii, 762
- 460 RABSON, S M Brucellosis, *Hygeia*, 1940, xviii, 983-986, 1019-1020
- 461 RANTZ, L A Suppurative arthritis due to a hemolytic streptococcus of the Lancefield group B, a case report, *ANN INT MED*, 1940, xiii, 1744-1747
- 462 RATHE, H W Rheumatic heart disease, with review of 95 cases, *Jr Iowa Med Soc*, 1940, xxx, 95-100
- 463 RAUCH, SOLOMON Transitory synovitis of the hip joint in children, *Am Jr Dis Child*, 1940, lxx, 1245-1265
- 464 RAVENNA, PAOLO A review of recent Italian work on rheumatism II Chronic rheumatism, *Ann Rheumat Dis*, 1940, ii, 1-18
- 465 RAWLINS, M The chemotherapy of gonorrhoea failures, their cause and prevention, *Brit Jr Ven Dis*, 1940, xvi, 232-236

- 466 RAY, M B The therapeutic pool, *Lancet*, 1940, 1, 683-685
- 467 READ, FRANCES E M, and GAULD, R L Studies in rheumatic disease IV The familial aggregation of rheumatic disease, tabulation of basic data relative to the occurrence of rheumatic manifestations in the families of 96 rheumatic index cases and their near relatives, *Am Jr Hyg*, 1940, xxxi, 124-126
- 468 REASER, E F Chorea of infectious origin, *South. Med Jr*, 1940, xxxiii, 1324-1328
- 469 REIMANN, H A, and HAVENS, W P Focal infection and systemic disease a critical appraisal, the case against indiscriminate removal of teeth and tonsils, *Jr Am Med Assoc*, 1940, cxiv, 1-6
- 470 Report on epidemiology of rheumatic infection in South Australia, *Med Jr Australia*, 1940, 1, 461-483
- 471 REYERSBACH, GERTRUDE, and KUTTNER, ANN G Studies on the auriculoventricular conduction time of normal children and of rheumatic children without signs of rheumatic activity, *Am Heart Jr*, 1940, xx, 573-585
- 472 ROBBINS, HERMAN, and DURANTE, M H A frequent diagnostic error in cases of acute rheumatic carditis, *Arch Pediat*, 1940, lvii, 216-225
- 473 ROBERTS, C J Rheumatic fever Types, diagnosis, and treatment, *Jr Oklahoma Med Assoc*, 1940, xxxiii, 15-18
- 474 ROBINSON, G Tuberculin reactions in ankylosing spondylitis compared with those in other rheumatic diseases, *Ann Rheumat Dis*, 1940, ii, 41-46
- 475 ROBINSON, J M Retropulsion of the lumbar intervertebral discs as a cause of low back pain with unilateral "sciatic" radiation, roentgenologic diagnosis, with special reference to iodology, *Am Jr Surg*, 1940, xlix, 71-88
- 476 ROLLSTON, HUMPHREY The history of rheumatism in Great Britain, *Brit Jr Rheumat*, 1940, ii, 189-195
- 477 ROPES, MARIAN W, ROSSMEISL, ELSIE C, and BAUER, WALTER The origin and nature of normal human synovial fluid, *Jr Clin Invest*, 1940, xix, 795-799
- 478 ROSEN, GEORGE The miner's elbow, *Bull Hist Med*, 1940, viii, 1249-1251
- 479 ROTH, G B Sulfapyridine—its nature and some theories of its action, *Med Ann District of Columbia*, 1940, ix, 153-159
- 480 ROTH, I R Clinical aspects of rheumatic fever in adults, *Bull New York Acad Med*, 1940, xvi, 514-524
- 481 ROTHBARD, SIDNEY Experimental arthritis in the albino rat produced by a Group A hemolytic streptococcus, *Proc Soc Exper Biol and Med*, 1940, xlv, 379-381
- 482 ROYLE, N D Operation for ankylosing knee joint, *Med Jr Australia*, 1940, 1, 410-411
- 483 RUHMANN, W Earliest book on rheumatism, *Brit Jr Rheumat*, 1940, ii, 140-162
- 484 RYANARSON, E H Hyperparathyroidism, *Med Clin North America*, 1940, xxiv, 1027-1033
- 485 SABIN, A B, and JOHNSON, BARBARA Search for microorganisms of the pleuropneumonia group in rheumatic and non-rheumatic children, *Proc Soc Exper Biol and Med*, 1940, xlv, 565-569
- 486 SABIN, A B, and WARRER, JOEL The therapeutic effectiveness of a practically non-toxic new compound (calcium aurothiomalate) in experimental, proliferative, chronic arthritis of mice, *Science*, 1940, xcii, 535-536
- 487 SALBERG, J B, and BRUNFT, W M Gonococcal arthritis in women, a study of thirty cases, *Med Rec*, 1940, cli, 294-296
- 488 SALSBERY, C R A contribution to the anatomy of the ulnar bursa, *Canad Med Assoc Jr* 1940 xliii, 430-432
- 489 SARMA P J The injection treatment of ganglions and bursae indications and limitations *Surg Clin North America*, 1940, xx, 135-140
- 490 SALZBERG, J B DE C M, and LAYMAN, V T Pathology of the intervertebral disk, *Arch Surg*, 1940, xl, 389-416
- 491 SCHMIDT, N K, and STANDER, H J True uric acid in hyperuricemia of pre-eclampsia and eclampsia *Proc Soc Exper Biol and Med*, 1940, xlv, 180

- 492 SCHAILIG, DOROTHY W Arthritis its treatment with undenatured bacterial antigens, *California and West Med*, 1940, *li*, 212-214
- 493 SCHIFLEY, C H, and HIGGINS, G M The effect of the administration of colchicine after partial removal of the liver, *Proc Staff Meet Mayo Clin*, 1940, *xv*, 536
- 494 SCHOTT, A Diagnostic problems in cases of chronic rheumatic heart disease, *Brit Jr Rheumat*, 1940, *ii*, 130-139
- 495 SCULL, C W Metabolic and dietetic considerations in the treatment of arthritis, *Med Clin North America*, 1940, *xxiv*, 1659-1671
- 496 SCULL, C W, and PEMBERTON, RALPH The formol-gel reaction in blood of patients with chronic rheumatoid diseases, *ANN INT MED*, 1940, *xiv*, 993-1000
- 497 SCULLY, F J Aciform treatment of rheumatic disorders, *Jr Arkansas Med Soc*, 1940, *xxxvi*, 225-227
- 498 SECHER, KNUD Vitamins as a supplement to sanocrysin in arthritis, *Lancet*, 1940, *i*, 735-736
- 499 SFDLÁČEK, K Gout and rheumatism, *Acta rheumatol*, 1939, *xi*, 5-14
- 500 SFN, S N A study of chorea with special reference to rheumatic chorea, *Indian Jr Pediat*, 1940, *vii*, 135-153
- 501 SHAW, L O, and McAILLISTER, M M Details of a proved technique for the culture of the gonococcus and its clinical value, *Urol and Cutan Rev*, 1940, *xlv*, 429-430
- 502 SHERWOOD, K K Physical therapy in arthritis, *Physiotherapy Rev*, 1940, *xx*, 134-137
- 503 SHERWOOD, K K Classification and treatment of chronic arthritis, *South Surgeon*, 1940, *iv*, 571-583
- 504 SHERWOOD, K K Newer drugs in treatment of arthritis, *Northwest Med*, 1940, *xxxix*, 452-454
- 505 SHINKAWA, T Experimental and clinical studies on absorption from diseased joints with uramin solution, *Nagoya Jr Med Sci*, 1939, *xiii*, 107, 197
- 506 SHIPLEY, A M Ossifying hematoma and allied conditions, *Arch Surg*, 1940, *xli*, 516-524
- 507 SIDEL, NATHAN, and ABRAMS, M I Treatment of chronic arthritis, results of vaccine therapy with saline injections used as controls, *Jr Am Med Assoc*, 1940, *cxiv*, 1740-1742
- 508 SILBERBERG, MARTIN, and SILBERBERG, RUTH Effects of prolonged injections of bovine anterior pituitary extract on bone and cartilage of guinea pigs, *Arch Path*, 1940, *xxix*, 355-367
- 509 SILBERBERG, MARTIN, and SILBERBERG, RUTH The effect of thyroidectomy and administration of anterior pituitary extract of cattle on the growth of cartilage and bone of immature guinea pigs, *Am Jr Path*, 1940, *xvi*, 505-524
- 510 SILBERBERG, MARTIN, and SILBERBERG, RUTH Changes in cartilage and bone of immature female guinea pigs due to undernourishment, with consideration of the processes of repair following period of refeeding, *Arch Path*, 1940, *xxx*, 675-688
- 511 SIMPSON, W M Brucellosis (undulant fever), *Ohio State Med Jr*, 1940, *xxxvi*, 1053-1060
- 512 SIMPSON, W M Brucellosis (undulant fever) In TICE, FREDERICK *Practice of medicine*, 1940, W F Prior Company, Inc, Hagerstown, Maryland, vol *iv*, chap *xxiv*, 99-108
- 513 SIMPSON, W M Artificial fever therapy In *Modern medical therapy in general practice*, 1940, The Williams & Wilkins Company, Baltimore, 492-528
- 514 SKEER, JACOB, and KAPLAN, A A Ehlers-Danlos syndrome, *Arch Dermat and Syph*, 1940, *xlii*, 450-455
- 515 SLOCUMB, C H Arthralgia and arthritis of lupus erythematosus, *Proc Staff Meet, Mayo Clin*, 1940, *xv*, 683-686
- 516 SLOCUMB, C H Differential diagnosis of periarticular fibrositis and arthritis, *Ann Rheumat Dis*, 1940, *ii*, 108-113

517. SMALL, J C · The treatment of chronic arthritis with microdosage of bacterial products, *Med Clin North America*, 1940, xxiv, 1717-1723
- 518 SMART, MORTON Physical medicine in war time, *Brit Jr Phys Med*, 1940, iii, 42-46
- 519 SMITH, C E Epidemiology of acute coccidioidomycosis with erythema nodosum ("San Joaquin" or "valley fever"), *Am Jr Pub Health*, 1940, xxx, 600-611
- 520 SMITH, E M, and LUTTERLOH, C H Spa therapy in rheumatic diseases, *Arch Phys Therap*, 1940, xxi, 141-143
- 521 SMYTH, C J, and FREYBERG, R H A study of the hereditary nature of gout, A preliminary report of two families, *Univ Hosp Bull, Ann Arbor*, 1940, vi, 62-63
- 522 SMYTH, C J, FREYBERG, R H, and LAMPE, ISADORE Roentgen therapy for rheumatoid arthritis of the spine (Marie-Strumpell arthritis, spondylitis Rhizomélisque), *Jr Am Med Assoc*, 1941, cxvii, 826-831
- 523 SMYTH, C J, FREYBERG, R H, and PECK, W S Roentgen therapy for rheumatic disease, *Jr. Am Med Assoc*, 1941, cxvi, 1995-2001
- 524 SNYDER, R G Arthritis—A neglected disease, *ANN INT MED*, 1940, xiii, 1317-1326
- 525 SNYDER, R G, and SQUIRES, W H A preliminary report on activated ergosterol, A form of high-dosage vitamin D in the treatment of chronic arthritis, *New York State Jr Med*, 1940, xl, 708-719
- 526 SOLOMON, W M Periarthritis of the shoulder, *Physiotherapy Rev*, 1940, xx, 323-327
- 527 SOLOMON, W M, and STECHER, R M Treatment of atrophic arthritis with artificial fever therapy, *Arch Phys Therap*, 1940, xxi, 339-342
- 528 SOTO-HALL, RALPH, and HALDEMAN, K O The diagnosis of neuropathic joint disease (Charcot joint), an analysis of forty cases, *Jr Am Med Assoc*, 1940, cxiv, 2076-2078
- 529 SPACKMAN, E W The roentgen aspects of chronic arthritis, *Med Clin North America*, 1940, xxiv, 1603-1619
- 530 SPEED, J S, and SMITH, HUGH Arthroplasty, a review of the past ten years, *Internat Abstr Surg*, 1940, lxx, 224-230
- 531 SPEFD, KELLOG Hip arthroplasty, with vitallium cap, *West Jr Surg*, 1940, xlviii, 101-105
- 532 SPRENGER, LOUISE T The need of establishing a home program for the convalescing rheumatic fever patient, *Occup Therap*, 1940, xix, 263-264
- 533 SPURLING, R G, and GRANTHAM, E G Neurologic picture of herniations of the nucleus pulposus in the lower part of the lumbar region, *Arch Surg*, 1940, xl, 375-388
- 534 SPURLING, R G, and GRANTHAM, E G Low back and sciatic pain caused by rupture of the intervertebral disc with or without herniation of the nucleus pulposus, *New Internat Clin*, 1940, s 3, iv, 251-266
- 535 STACK, J K · Spontaneous hemarthrosis due to synovial granuloma, *Jr Bone and Joint Surg*, 1940, xxii, 735-737
- 536 STANFORD, W R, and GEYERHAIN, GEORGE Undulant fever, report of two cases, *North Carolina Med Jr*, 1940, i, 321-324
- 537 STARK, LUCY Rheumatic heart disease, *Med Rec*, 1940, cli, 354-357
- 538 STECHER, R M. Heberden's Nodes The incidence of hypertrophic arthritis of the fingers, *New England Jr Med*, 1940, ccxxii, 300-308
- 539 STECHER, R M, and SOLOMON, W M Treatment of gonorrheal arthritis, *Ohio State Med Jr*, 1940 xxxvi, 24-26
- 540 STEIN BROCKF, OTTO, McEACHERN, G C, LAMOTTA, E P, and BROOKS, FREEMAN Experience with cobra venom in the arthralgias and related conditions, *Jr. Am. Med Assoc*, 1940, cxiv, 318-322
- 541 STEINLETT, ARTHUR Orthopedic complications of brucellosis, *Jr Iowa Med Soc*, 1940, xxx 256-257
- 542 STEIN, A · A case of gonococcal arthritis, *Brit. Med Jr*, 1940, ii, 117.
- 543 STEIN, N S Acute rheumatic fever, *Memphis Med Jr*, 1940, xv, 181-182

- 544 STICKNEY, J M Systemic involvement in disseminated lupus erythematosus, *Proc Staff Meet Mayo Clin*, 1940, xv, 680-681
- 545 STICKNEY, J M, and KEITH, N M Renal involvement in disseminated lupus erythematosus, *Arch Int Med*, 1940, lxxvi, 643-660
- 546 STILES, M H Sedimentation rate and nonfilament-filament ratio in low grade chronic illness, a statistical analysis of 292 cases, *Arch Int Med*, 1939, lxxiii, 664-678
- 547 STILES, M H, and CHAPMAN, G H Probable pathogenic streptococci and staphylococci in chronic low grade illness, an analysis of their frequency in three hundred and ninety-five cases, *Arch Otolaryng*, 1940, xcxi, 458-466
- 548 STILES, M H, DIRICKX, E F, and STILES, M T The normal nonfilament-filament count and its relation to the Schilling count, *Am Jr Clin Path*, 1940, x, 783-791
- 549 STIMSON, H Bursitis, *Am Jr Surg*, 1940, l, 527-533
- 550 STONE, S Treatment of Sydenham's chorea by fever and vitamin B therapy, *New England Jr Med*, 1940, cccxxxiii, 489-496
- 551 STOOKEY, B Compression of spinal cord and nerve roots by herniation of the nucleus pulposus in the cervical region, *Arch Surg*, 1940, xl, 417-432
- 552 STOTT, A W, and COPEMAN, W S C Chronic meningococcal septicaemia, associated with an outbreak of cerebrospinal fever, *Lancet*, 1940, i, 1116-1118
- 553 STRAUSS, S G Intradermal lactalbumin in the treatment of chronic arthritis, a preliminary report, *Med Rec*, 1940, cli, 370-372
- 554 STROUD, W D, and TWADDLE, P H Fifteen years' observation of children with rheumatic heart disease, *Jr Am Med Assoc*, 1940, cxiv, 629-634
- 555 STRUTHERS, R R Rheumatic heart disease in adolescence, *Canad Med Assoc Jr*, 1940, xlii, 128-133
- 556 STUMP, J P The prevention of arthritic deformities by early orthopedic management, *ANN INT MED*, 1940, xiv, 87-99
- 557 SWAN, HENRY Effect of cholecystogastrostomy on cinchophen-produced ulcer in dogs, *Arch Surg*, 1940, xli, 569-584
- 558 SWETT, P P, BENNETT, G E, and STREET, D M Pott's disease The initial lesion, the relative infrequency of extension by contiguity, the nature and type of healing, the rôle of the abscess, and the merits of operative and non-operative treatment, *Jr Bone and Joint Surg*, 1940, xxii, 878-894
- 559 SWIFT, H F Features which suggest public health consideration of rheumatic fever, *Bull New York Acad Med*, 1940, s 2, xvi, 501-513
- 560 SWIFT, H F Rheumatic heart disease, pathogenesis and etiology in their relation to therapy and prophylaxis (John H Wyckoff lecture), *Medicine*, 1940, xix, 117-440
- 561 SWIFT, H F Public health aspects of rheumatic heart disease, incidence and measures for control, *Jr Am Med Assoc*, 1940, cxv, 1509-1518
- 562 SWIFT, W E End results of the spine-fusion operation for tuberculosis of the spine, *Jr Bone and Joint Surg*, 1940, xxii, 815-823
- 563 SYDENHAM, THOMAS A treatise of the gout and dropsy, *Med Classics*, 1939, iv, 354-397
- 564 TALBOTT, J H Serum urate in relatives of gouty patients, *Jr Clin Invest*, 1940, xix, 645-648
- 565 TARSY, J M Clinical experiences with gold salts in the treatment of rheumatoid arthritis, *New York State Jr Med*, 1940, xl, 1185-1191
- 566 TATLOW, W F T Abortus fever treated with sulphamidamide, *Brit. Med Jr*, 1940, i, 1056
- 567 TAYLOR, N S Sulphapyridine in the treatment of acute urethritis, *Brit Med. Jr*, 1940, i, 88-89
- 568 TERRAY The chemical aspect of gout, *Rheumatism*, 1940, ii, 31-35
- 569 TERRY, L L, and WORK, J L Trichinosis of the myocardium, report of a case, with autopsy findings, *Am Heart Jr*, 1940, xix, 478-485

- 570 THOMAS, R B Report of committee for survey of research on gonococcus and gonococcal infections, from January, 1936 to January, 1938, Ven Dis Inform, 1939, Supp 8, pp 1-78
- 571 THOMPSON, EDWARD The treatment of rheumatic heart disease, Nebraska Med Jr, 1940, xxv, 58-59
- 572 THOMPSON, H C Gout, North Carolina Med Jr, 1940, 1, 379-382
- 573 THOMSON, ST C Engraved portrait of a centenarian, published in 1806, Proc Roy Soc Med, 1940, xxxiii, 774
- 574 THORNDIKE, AUGUSTUS, JR Knee injuries incident to sports and recreation, Am Jr Surg, 1940, xlvii, 542-551
- 575 THORNDIKE, AUGUSTUS, JR Myositis ossificans traumatica, Jr Bone and Joint Surg, 1940, xxii, 315-323
- 576 TIPPETT, G O The use of plaster splintage in the treatment of arthritis, Brit Jr Rheumat, 1940, 11, 195-202
- 577 TITUS, N E The treatment of chronic fibromyositis with electrotherapy, Med Rec, 1939, cl, 428-430
- 578 TODD, E W, COBURN, A F, and HILL, A B Antistreptolysin S titres in rheumatic fever, Lancet, 1939, 11, 1213-1217
- 579 TRASOFF, ABRAHAM, and SCARF, MAXWELL Periarthritis nodosa and asthma, case report, Jr Allergy, 1940, xi, 277-280
- 580 TRAUTMAN, J A Hyperpyrexia—its indications and complications, evaluation of results based on 5,500 fever sessions, New Orleans Med and Surg Jr, 1940, xcii, 630-637; Hosp News, 1940, vii, 1-15
- 581 VAN HAZEL, WILLARD Joint manifestations associated with intrathoracic tumors, Jr Thoracic Surg, 1940, 1, 495-505
- 582 VEST, S A, and PARKER, D S, JR The use of the disulfanilamides in gonorrhea, Am Jr Syph, Gonorr, and Ven Dis, 1940, xxiv, 344-359
- 583 WALKER, M A, and ALLEN, L G Air in knee after trauma, Radiology, 1940, xxxiv, 239
- 584 WALLGRFN, ARVID Acute rheumatic fever in children, Irish Jr Med Sci, 1939, s 6, 793-801
- 585 WAISH, B. J, BRIAND, E F, and JONES, T D Pure mitral stenosis in young persons, Arch Int Med, 1940, lxxv, 321-327
- 586 WASSERSUG, J D Tuberculosis of the greater trochanter and trochanteric bursae, Jr Bone and Joint Surg, 1940, xxii, 1075-1079
- 587 WASSON, V P, and BROWN, E E Immunization against rheumatic fever with hemolytic streptococcus filtrate, Am Heart Jr, 1940, xx, 1-11
- 588 WATSON, E M The effect of adrenal cortical extract on the serum phosphatase in chronic arthritis, Endocrinology, 1940, xxvii, 521-522
- 589 WEFER, ALANSON Subdeltoid bursitis, Arch Surg, 1940, xli, 554-556
- 590 WEIL, S D, SMITH, E M, KING, L E, and WOORON, W T An analysis of the routine sedimentation rate in 1,000 admissions to the arthritic clinic, Levi Memorial Hospital, Jr Arkansas Med Soc, 1940, xxxvi, 241-243
- 591 WEILAND, A H, and BURBACHER, C R Bursitis about the shoulder, South Surgeon, 1940, ix, 26-33
- 592 WERNER, T B Arthritis and para-arthritis treated with the roentgen ray, report of 161 cases, Am Jr Roentgenol, 1940, xliii, 416-424
- 593 WEINER, A L Disseminated lupus erythematosus treated by sulfanilamide, report of four cases, Arch Dermat and Syph, 1940, cli, 534-544
- 594 WEIL, THELMA An unusual spirochete recovered from the blood in arthritis, Am Jr Clin Path, 1940, x, 460-466
- 595 WEINSTEIN, K R Symptoms and diagnosis of joint diseases, Jr Iowa Med Soc, 1940, xxx, 467-469

- 596 WESTCOTT, W I Special therapeutic agents in arthritis, *Med Clin North America*, 1940, **xv**, 1725-1733
- 597 WILE, U J, and HOIVAN, H H Acute disseminated lupus erythematosus Its treatment with sulfamidamide and allied products, *Arch Dermat and Syph*, 1940, **xli**, 1059-1072
- 598 WILLARD, J H, and STRAWBRIDGE, R R Gallbladder infections as a factor in arthritis, *Med Clin North America*, 1940, **xv**, 1709-1716
- 599 WILLIAMS, A W Heart disease in native population of Uganda, rheumatic heart disease, *East African Med Jr*, 1939, **xvi**, 341-361
- 600 WILLIAMS, I H L Manipulation of joints, *Jr Roy Army Med Corps*, 1940, **lxxiv**, 86-91
- 601 WILLIS, V N B Chemotherapy in the treatment of gonorrhoea in males, *Med Jr Australia*, 1940, **i**, 82-85
- 602 WILMOTH, C L Surgical conditions of the knee joint, *Rocky Mountain Med Jr*, 1940, **xxvii**, 672-676
- 603 WILSON, G S, and MAIER, IRENE Treatment with sulphapyridine (M & B 693) of guinea-pigs infected with *Brucella abortus*, *Brit Med Jr*, 1940, **i**, 47-50
- 604 WILSON, P D The painful shoulder, *Brit Med Jr*, 1939, **ii**, 1261-1265
- 605 WILTSIF, J W The bowel as a focus of sepsis in chronic rheumatic disease, *Post-Grad Med Jr*, 1940, **xvi**, 51-60
- 606 WINSBURY-WHITE, H P Chronic focal infection in the genito-urinary apparatus, *Rheumatism*, 1940, **ii**, 9-22
- 607 WINTFR, H G Further notes on the treatment of gonorrhea with the sulphonamide group of drugs, *Jr Roy Army Med Corps*, 1940, **lxxv**, 1-7
- 608 WOOD, J K W Undulant fever diagnosis and prevention, *Pennsylvania Med Jr*, 1940, **xliii**, 459-464
- 609 WOODHALL, BARNES, RANEY, R BEVERLY, and VAUGHAN, W W Low back pain and sciatica with special reference to rupture of the intervertebral disc, *North Carolina Med Jr*, 1940, **i**, 94-101
- 610 WOODS, R S The organization in emergency medical services of ministry of health, *Brit Jr Phys Med*, 1940, **n s 3**, 102-103, personal communication to the authors
- 611 WOOLFERT, O C Acute rheumatic fever, etiology, *Rev Med Progress*, 1940, 59-60
- 612 WRIGHT, WALE The results of sulfamidamide therapy in treatment of gonorrhea, *Journal-Lancet*, 1940, **lx**, 21-25
- 613 WYMAN, J F Advantages of institutional care and physical therapy in chronic arthritis, *Arch Phys Therap*, 1940, **xxi**, 301-304
- 614 YOUNG, J Relaxation of pelvic joints in pregnancy, pelvic arthropathy of pregnancy, *Jr Obst and Gynaec Brit Emp*, 1940, **xlvii**, 493-524
- 615 ZEITER, W J Some applications of medical diathermy, *Med Clin North America*, 1940, **xxiv**, 543-553
- 616 ZEITER, W J Clinical application of short wave diathermy, *Cleveland Clin Quart*, 1940, **vii**, 184-190

Books, 1939-1940

These books appeared during 1939-1940 but were *not* reviewed herein

- 1 BRUUN, EGON Experimental investigations in serum allergy with reference to the etiology of rheumatic joint diseases, 1940, Munksgaard, London Oxford, 229 pp
- 2 COMROE, B I Arthritis and allied conditions, Lea & Febiger, Philadelphia, 1940, 752 pp
- 3 JEFFERY, CLEMENT Rheumatism its causes, prevention and treatment, Muller, London, 1940, 64 pp
- 4 MENNELL, J B Physical treatment by movement, manipulation and massage, Ed 4, 1940, Blakiston, Churchill, London, 682 pp

- 5 SANDS, OLIVE F. Physiotherapy, 1939, Faber, s 2, d 6, 79 pp
- 6 VANDER, ADRIAN Rheumatism and gout its cause and cure, Chem Pub Co, 1940, 111 pp
- 7 WIBERG, GUNNAR Studies on dysplastic acetabular and congenital subluxation of the hip joint with special reference to the complication of osteo-arthritis Acta Chirurgica Scandinavica LXXXIII, Supplementum LVIII, 1939, Norstedt, Stockholm, 135 pp
- 8 WILSON, MAY G Rheumatic fever Studies of the epidemiology, manifestations, diagnosis, and treatment of the disease during the first three decades, 1940, The Commonwealth Fund, New York, 595 pp

CASE REPORTS

ECHINOCOCCUS CYST OF THE HEART; REPORT OF A CASE*

By C J ATTWOOD, M.D, WILLIAM H SARGENT, M.D., and
FLETCHER TAYLOR, M.D., F.A.C.P., *Oakland, California*

THE case here reported presents a most unusual radiological finding in the heart which we believe to be due to a solitary echinococcus cyst situated in the left ventricle †

R S, a white female of 57 years, complained of occasional attacks of palpitation and a gradually increasing sensation of "heaviness" in the left chest for four years. Her past history was not remarkable. She had never been outside the United States and since the age of five had resided in California. For the past 15 years she had had

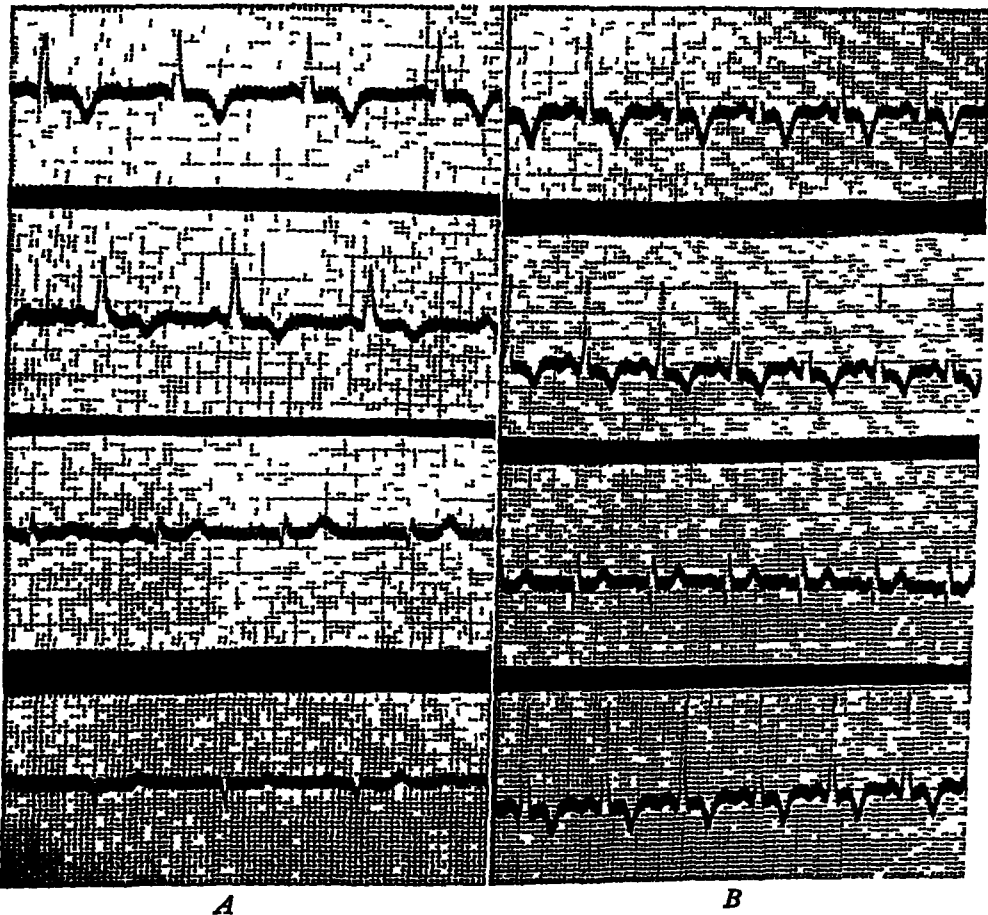


FIG 1 Electrocardiograms A Made July 18, 1938, B Made July 8, 1939

* Received for publication October 16, 1939
From Samuel Merritt Hospital, Oakland, California

† We are indebted to Dr J M McCullough for his permission to examine and report this case.

at least one pet dog which she had permitted to sleep on her bed. At no time had there been severe thoracic pain nor had there been any evidence of cardiac decompensation. She had not been obliged to limit her activities in any way. An electrocardiogram made a year previously (figure 1, *A*) showed evidence, however, of a considerable degree of myocardial impairment. A recent electrocardiogram (figure 1, *B*) showed an increase in the cardiac rate as compared with the previous tracing but did not appear to indicate increasing myocardial damage. At the present time a careful physical examination failed to reveal any evidence of organic pathological change. Blood count and urinalysis were well within the normal. The Wassermann test was negative. The blood pressure was 145 mm of mercury systolic and 90 diastolic. Skin tests made with hydatid cyst fluid from a recent case and with similar material obtained from Dr T B Magath of the Mayo Clinic were negative. In spite



FIG 2 Two meter postero-anterior view. Note oval, calcified shadow in left side of heart. A thin layer of the myocardium can be seen around the left side of the wall of the calcified shadow.

of the negative skin reaction, however, the roentgen-ray findings in the heart (figures 2, 3 and 4) led us to conclude that this patient was suffering from a solitary echinococcus cyst of the left ventricle.

A two meter postero-anterior projection of the chest (figure 2) showed an oval shadow measuring 6.5 by 8 cm with a periphery of calcium density situated in the

region of the left ventricle. By viewing this shadow from all directions fluoroscopically and by taking films of the heart in lateral and oblique positions, two of which are reproduced in figures 3 and 4, it was possible not only to show that the object responsible for this unusual shadow was ovoid in form but that its position was within the wall of the left ventricle. A second roentgen-ray examination, made almost a year after the first examination of this patient, showed no discernible change either in the heart or in the calcified body situated within it. We know of no pathological process involving the heart which could produce these radiological findings unless it be an *echinococcus* cyst. A careful search failed to reveal any evidence of additional cysts located elsewhere in the body.*



FIG 3 Left posterior oblique view made with the Buckey diaphragm

Hydatid cysts of the heart were reported during the seventeenth and eighteenth centuries by Thebesius, Rolfincke and Fanton¹ and early in the nineteenth century by Portal, Dupuytren, Meckel, Price and Morgagni². It has been pointed out by Mills,³ however, that the term "hydatid disease" was rather loosely used at the time of these early reports and not always restricted to cases in which the pathological changes were caused by the larval or cystic stages of *Taenia echinococcus*, the dog tapeworm. For this reason it seems unlikely that

* On Nov 28, 1941, the patient was following her normal activities with no additional symptoms

all the lesions described by these early writers were actually the result of echinococcus disease

The first paper of significance concerning this rare and interesting condition seems to be that of Griesinger⁴ which appeared in the German literature in 1846. Griesinger collected and reported 15 cases which at autopsy were found to have echinococcus disease involving the heart. In 1858 Budd⁵ reported five additional cases. One of these, a female of 23 years, was found at autopsy to have a cyst the "size of an orange, full of daughter cysts" situated in the right ventricle. Neisser⁶ found 29 reported cases in 1877, and by 1905 Grulee⁷ was able to find 55 cases, 26 males and 19 females, in whom there was echinococcic in-



FIG 4 Left anterior oblique view made with the Buckey diaphragm

volvement of the myocardium. Their cases ranged in age from seven to 73 years, 41 per cent occurring between the ages of 15 and 25 years. In only 15 of the 55 cases was the heart alone involved. Grulee reported in detail the case of a 27 year old female who was found at autopsy to have an echinococcus cyst the size of a pigeon's egg in the posterior wall of the right ventricle. This cyst had ruptured into the ventricle and multiple embolic cysts were found scattered throughout both lungs, several communicating directly with branches of the pulmonary artery.

Davis⁸ in 1916 was able to find in the literature 105 cases of myocardial involvement in echinococcus disease. In 48 of these cases intracardiac rupture had occurred, the right side of the heart being involved in 28, the left side in 20

Mills,⁷ reviewing the literature in 1922, was unable to find a single case in which the correct diagnosis was made prior to autopsy. He reported the case of a female of 36 years in whom autopsy revealed an echinococcus cyst measuring 4 by 5 cm situated in the apex of the right ventricle. Four additional cysts were found in the right lung. As far as we have been able to determine the case reported by Mills was the third to be reported from the United States.

In the 17 years following the publication of Mills' paper we have been able to find reference in the literature to 26 additional cases, none of which, however, occurred in North America. Between 1924 and 1929 Hynd,⁸ Finny,¹⁰ Heilmann,¹¹ and Corkill¹² reported cases in the British Medical Journal. One of



FIG 5 Postero-anterior film of the chest showing an echinococcus cyst of the heart. Diagnosis proved by operation. Reproduced by permission of Dr Blondeau

these cases occurred in England. The others occurred in India, Bagdad and South Africa. In the two cases reported by Corkill and Heilmann the cyst was found to occupy the interventricular septum. These hearts have both been preserved. One is at the Royal Iraq College of Medicine at Bagdad, the other in the Museum of the South African Institute of Medical Research at Johannesburg.

A case of multiple echinococcus cysts of the heart was reported by Bacaloglu et al.¹³ in 1929. This patient, a male of 27 years, was found at autopsy to have a heart weighing 930 grams, or approximately three times normal. An echinococcus cyst 8 cm in diameter was found to involve the left auricle and communicated with the auricular lumen. This cyst contained 50 or more daughter cysts each about the size of a pea. Three other cysts of smaller size were situated in the wall of the left ventricle. Two of the ventricular cysts were multilocular.

Examination of the brain showed numerous areas of infarction. Emboli were also found in the liver, spleen, kidneys and adrenal glands. Another case showing secondary involvement of the central nervous system has been reported by Morquio¹⁴. A child of 11 years, this patient suffered from headache, photophobia, strabismus and mental impairment. No abnormality of the heart could be found on physical examination. The clinical course was one of progressive general failure. At autopsy a small echinococcus cyst was found in the wall



FIG 6 Lateral film of the chest shown in figure 5. Reproduced by permission of Dr. Blondeau.

of the left ventricle which communicated with the ventricular lumen. Nine secondary cysts were found in the brain and two in the spleen.

A most interesting case has recently been reported from Algeria by Blondeau¹⁵ who has kindly given his consent to the reproduction of his excellent roentgenograms (figures 5 and 6). This was proved to be a case of echinococcus disease of the heart by surgical intervention. The calcifications seen at the inferior and left borders of the cardiac shadow probably represent an "echinococcus seeding" of the pericardium. Dr. Blondeau calls particular attention to the heavy calcification of the cardiac echinococcus cyst which he reported and

points out that in our case the cyst wall was also heavily calcified¹⁶ This he logically supposes to be due to the resistance offered to the growth of the cyst by a relatively dense tissue such as the myocardium He considers heavy calcification a very important radiographic sign, "probably even pathognomonic" of a cardiac rather than a pulmonary origin, pointing out that pulmonary echinococcus cysts are rarely calcified at all "while hepatic and muscular cysts grow in resistant tissue and calcify themselves strongly"

It is noteworthy that in the cases of cardiac echinococcosis reported in the literature little or no mention is made of calcification in the cyst wall except in the case reported by Blondeau Whether or not calcium was looked for could not be determined from the reports In spite of this fact we are inclined to agree with Blondeau that a spherical mass with a calcified periphery in the heart is most likely to be an echinococcus cyst and it seems justifiable to conclude in the case here presented that the findings in the left ventricle were due to such a cyst We do not feel that the presence of a negative skin reaction completely rules out such a diagnosis According to Stitt¹⁷ the intradermal skin test is negative in 13 per cent of cases of echinococcosis Moreover, since the condition appeared to have remained unchanged for at least a year and probably longer, and since negative skin tests were obtained, it seemed likely that this was a dead or stationary cyst

BIBLIOGRAPHY

- 1 Cited by Mills, H W³
- 2 Cited by Mills, H W³
- 3 MILLS, H W Hydatid cysts of the heart, with report of a case, *Surg, Gynec and Obst.*, 1922, xxxv, 455-461
- 4 GRIESINGER, W Ueber Acephalocysten am Herzen, *Arch f physiol Heilk*, Stuttg, 1846, v, 280-287
- 5 BUDD, GEORGE Hydatid tumour in the apex of right ventricle of the heart, *Trans Path Soc. of London*, 1859, x, 80-83
- 6 NEISSER, A Die Echinococcen-Krankheit, 1877, Berlin
- 7 GRULEE, C G Echinococcus disease of the heart, with report of a case, *Surg, Gynec and Obst.*, 1905, 1, 328-335
- 8 BOPPE, MME MARCEL (née EDMÉE DEVÉ) L'échinococcose pulmonaire métastatique, 1916, Paris No 16
- 9 HYND, D Echinococcus cyst of the heart, *Brit Med Jr*, 1924, ii, 277
- 10 FINNY, C M Echinococcus cyst of the heart, *Brit Med Jr*, 1924, ii, 465
- 11 HEIMANN, H L Hydatid cyst of the heart, *Brit Med Jr*, 1928, i, 801
- 12 CORKILL, N L Hydatid cyst of the heart, *Brit Med Jr*, 1929, ii, 622
- 13 BACALOGLU, C, BALAN, N, BALLIF, L, and VASILESCU, C Le kyste hydatique du coeur, *Ann de Med*, 1929, xxvi, 242-268
- 14 MORQUO, L Kyste hydatique primitif du myocarde overt dans le ventricule gauche, *Arch de Med des Enfants*, 1934, xxxvii, 90-96
- 15 BLONDEAU, A, LAUPRETRE, and MIRAMOND, J Kyste hydatique du coeur Particularites de l'image radiologique, *L'Algerie Med*, 1938, xlii, 299-301
- 16 BLONDEAU, A Personal communication
- 17 STITT, E R *Diagnostics and treatment of tropical diseases*, 1929, P Blakiston's Son and Co, Philadelphia

SENSITIVITY TO PEANUT OIL WITH THE REPORT OF A CASE*

By FRANCIS H CHAFEE, M D , F A C P , *Providence, Rhode Island*

SINCE Keeney¹ in 1938 first reported the use of a slowly absorbed epinephrine preparation, allergists have found that the use of epinephrine in oil is of great value in controlling intractable asthma. Epinephrine in peanut oil is now available commercially. Although there are few reports in the literature definitely indicating that peanut oil may act as an atopen, there are records of unusual reactions to this preparation.

In 1939 Keeney² reported one instance in which urticaria developed after daily use of epinephrine in peanut oil for six weeks. This occurred along with a flare-up of an old sinusitis, and whether a true allergic reaction had occurred was never determined. Palpitation, nervousness, and other reactions probably due to epinephrine itself were reported by Keeney,² and by Murphy and Jones.³ Cohn⁴ in 1939 reported a vesicular urticarial reaction that lasted for two days in one patient, and in another a local redness that persisted for 18 hours. Neither of these cases reacted to a skin test to peanut oil.

Peanut oil is a common vehicle for hormonal products, and with their widespread use it is surprising that more untoward reactions are not reported. Levi-son and Harrison⁵ in 1939 reported a papular erythematous rash after the use of theelin. Scratch tests were negative, but intradermal skin tests with peanut and cotton seed oils gave an immediate reaction to both. A few days later scattered areas appeared similar to the original eruption. Davis⁶ reported a shock-like reaction to injections of estrogenic preparations. Skin tests with the pure oils were not done, but positive reactions to the products themselves were obtained. Eating peanuts caused a gastrointestinal upset in this patient.

CASE REPORT

A 32-year-old colored housewife entered the Allergy Clinic of the Rhode Island Hospital in March 1939 with a history of hay fever and asthma for the preceding nine years, occurring from August 15 to the time of frost. Her asthma was severe enough to have caused many hospital entries during the fall months. Family history showed the daughter to be highly allergic. Skin tests were positive to ragweed and timothy. She was given preseasonal ragweed therapy only. During June and July she had mild wheezing, and with the onset of the ragweed season her asthma became severe. Epinephrine, 1:1000 solution, gave considerable though temporary relief. During September her asthma continued, and aminophyllin, 0.5 grams intravenously, was necessary on several occasions. On September 19 she visited the Accident Room of the Rhode Island Hospital in a severe asthmatic state. Adrenalin in peanut oil was administered intramuscularly for the first time. A cramp-like pain at the site of injection immediately occurred, lasting an hour or two, and four hours later the site was reddened and raised over an area two inches across. It was described by the patient as being like a "bee sting" and lasted four to five days. Due to the continuation of asthma, the patient administered adrenalin in peanut oil to herself at least 10 times in the course of the next three weeks. Each injection not only gave a similar local reaction, but all previous sites flared up. Complete relief from asthma was not obtained, but her symptoms were ameliorated by adrenalin in peanut oil. Finally she

* Received for publication June 10, 1940.

was forced to discontinue the drug because of pain at the site of injection and the development of a generalized urticaria which lasted for 24 hours. Epinephrine in sesame oil was then administered on 12 different occasions with no ensuing reaction. Good therapeutic results were obtained. On November 27, when asthma-free, the patient was skin tested in the Clinic by the scratch and intradermal methods with adrenalin in peanut oil, theelin in peanut oil, and epinephrine in sesame oil. Positive reactions were obtained in each instance to the peanut oil products, the erythema being at least one-half inch in diameter and persisting for over 24 hours. Further questioning at that time elicited the fact that the patient avoided eating peanuts as she thought that they made her wheezy. A scratch test to peanuts, however, was negative. Pure peanut oil was obtained through the courtesy of Parke Davis & Company, and the patient was tested with this on February 23, 1940. Again positive reactions were obtained by the scratch and intradermal methods. Eight days later they were still strongly positive.

SUMMARY

A case is presented in whom there was an allergic reaction to peanut oil confirmed by skin test. A review of the literature is given.

REFERENCES

- 1 KELLER, E. L. Slowly absorbed epinephrine preparation, preliminary report, Bull Johns Hopkins Hosp, 1938, lxi, 227
- 2 KELLER, E. L., PIERCE, J. A., and GAY, L. N. Epinephrine in oil, a new slowly absorbed epinephrine preparation, Arch Int Med, 1939, lxix, 119
- 3 MURPHY, J. A., and JONES, C. A. Slow epinephrine in the treatment of chronic asthma, Jr Allergy, 1939, x, 215
- 4 COHN, J. Unusual reactions to slow epinephrine, Jr Allergy, 1939, x, 459
- 5 LEVISON, L. A., and HARRISON, J. J. Dermatitis following Theelin, Jr Am Med Assoc, 1939, cxiii, 2055
- 6 DAVIS, E. S. Correspondence, Jr Am Med Assoc, 1940, cxiv, 1285

EDITORIAL

THE DAYS AHEAD

WITH the declaration of war the long months of uncertainty and disagreement have ended like a dark dream and we face our enemies a strong and united Nation. The road to victory may be long, and progress will be won only with toil and anguish. Nor when military victory comes can we be content. The task goes on beyond that day when our opponents have surrendered their arms. The test of our true greatness as a Nation will be the establishment and the enforcement of a just and a lasting peace. If we and our allies should fail once more in the holding of that precious gift of peace then we would be unworthy of the men who fought and died.

The medical men in war assume heavy burdens, but they are already disciplined. Long hours, emergencies, panic, tears and blood are no new acquaintances to the doctor. We have a high tradition of service in wartime and we shall rise equal to it. Those who serve with troops in the forward zone, those who staff the military hospitals, and those who carry double loads in civilian practice will all be playing their part in winning this war. Let us each be sure where our duty lies and count no cost too great for the doing of it.

Above all when victory has been won in the field let us who will have seen the bloody and broken bodies of our wounded and our dead, remember their right to a peace that will be a fitting monument to their valor.

REVIEWS

A Manual of Allergy By MILTON B COHEN, M D 156 pages, 19 × 12 cm Paul B Hoeber, Inc, New York City 1941 Price, \$2 00

This volume is small, practically of pocket size, is simply but attractively bound, and typographically quite satisfactory. There are 143 pages of text which are clearly and logically divided into 15 chapters.

A brief but lucid presentation of general principles requires a nice selection of facts. Dr Cohen has accomplished this difficult feat as well as or better than any other author known to the reviewer.

However, not as much can be said for this book as a manual, which term suggests its use as a guide for the practical application of allergic diagnostic and therapeutic methods. The failure of the volume along these lines is suggested by the fact that the entire subject of bronchial asthma is covered in 13 pages of this small volume. The reviewer feels that all attempts at over simplification in this highly technical subject are doomed to failure.

As an attempt to etch in clearly and simply a background of information about a complex subject the book is more than successful. As an attempt to produce a simplified manual of allergy it is a failure, not because of the author's shortcomings, but because he has attempted the impossible.

H M B

Nitrous Oxide-Oxygen Anesthesia By F W CLEMENT, M D 274 pages, 24 × 15 5 cm Lea and Febiger, Philadelphia 1939 Price, \$4 00

"This volume is dedicated as a memorial tribute to the life work and achievements of E I McKesson, M D, F I C A in the specialty of anesthesia" and sets forth his philosophy and the technic of methods for the use of nitrous oxide and oxygen which he worked out during his lifetime. It is an authoritative treatise on this method of anesthesia, but its value as a practical guide for others is decreased by the fact that in the detailed description of technic the use of the McKesson machine only is described.

A complete explanation and rationalization of the signs of nitrous oxide-oxygen anesthesia are given. The importance of respiration and muscular signs is stressed, while phonation and color are shown to be deceptive and unreliable as they bear no relation to the depth of anesthesia in different individuals. Evaluation of the patient as an anesthetic risk, premedication, charting and signs of approaching shock are well presented.

The rôle of carbon dioxide in respiration is treated in a most thorough manner. The author shows that there is "no fixed relationship between cyanosis and physiological anoxemia." The famous "secondary saturation" is carefully described, explained and declared to be less dangerous than essential oxygen want during prolonged deep narcosis.

Dr Clement reiterates the importance of a clear airway and shows that obstruction to breathing causes alterations of the normal physiologic processes. His methods of treating respiratory obstruction are rational and simple and show great clinical knowledge. The chapter on endotracheal anesthesia contains a series of very helpful anatomical sketches showing the method of intubation by either the nasal or oral route with or without a laryngoscope. Although the author gives elaborate instruction for administering nitrous oxide-oxygen for major abdominal operations,

he admits that even the McKesson technic in his hands will not produce the relaxation obtained with ether or spinal anesthesia

There is no doubt left in the reader's mind of the clinical ability and knowledge of the author in the administration of nitrous oxide-oxygen anesthesia. His presentation of the subject is most convincing. The book is a fitting tribute to the late Dr McKesson and should, as intended, preserve for anesthetists the knowledge which he so painstakingly acquired

M J N

Dermatologic Therapy in General Practice By MARION B SULZBERGER, M D, and JACK WOLF, M D. 680 pages; 21 X 14.5 cm Year Book Publishers, Inc, Chicago 1940 Price, \$4.50

This book should prove to be very helpful to physicians who are not well acquainted with dermatologic therapeutics. The material is well selected, the arrangement is well planned, and the book is easily readable. The methods of treatment of the more common dermatoses are presented in a practical manner. The treatments for several rare dermatoses, such as Riehl's melanosis, erythroste pigmentaire peribuccale, epidermodysplasia verruciformis, and xeroderma pigmentosum are included, whereas the reader is referred to pediatric textbooks for descriptions of the treatment of impetigo of the newborn, and the treatment of the jigger or harvest mite is omitted from the index and referred to only briefly in the text. At the moment treatment of the latter disease is an important consideration of medical officers in the army.

Local anesthetics are recommended for treatment of pruritus ani and vulvae. The reviewer does not share the authors' opinion of their usefulness, and they often act as sensitizers. Some of the proprietary remedies and the "sulfa" drugs now recommended for topical applications had not been in use sufficiently long for a proper appraisal of their worth when the book was published. The chapters on syphilis are very well presented but suffer from the brevity of the usual short textbook. The statement that aldarone is preferable to tryparsamide is the authors' opinion and not a time tested fact.

None of the criticisms mentioned are sufficient to prevent this book from being one of the most practical, modern treatises on the therapy of skin diseases.

F. A. E.

Roentgen Interpretation By GEORGE W HOLMES, M D, and HOWARD E RUGGLES, M D. Sixth Edition, thoroughly revised. 364 pages, 24 X 15.5 cm Lea and Febiger, Philadelphia 1941 Price, \$5.00

What has been said about previous editions of the book can be said again about this edition. All radiologists of this country, and many in foreign lands, are familiar with "Holmes and Ruggles". The comprehensiveness and simplicity of this volume on roentgen interpretation have also made it popular with specialists in other fields. The purpose of the first edition in 1919 was to furnish "practical aid to those in search of a working knowledge of roentgen interpretation". Subsequent editions have kept the working knowledge up to date.

The sixth edition is not very unlike those preceding. The subject matter and illustrations have been reviewed, some of the latter having been replaced. Included in this volume are comments on new procedures developed in the past few years such as visualization of the heart chambers, body section roentgenology, spot-film gastro-intestinal work, Miller-Abbott intubation of the intestinal tract, and others. The bibliography has also been revised and brought up to date. Those who are familiar with previous editions will still find the sixth edition in accord to their libraries.

W L K.

Biology of the Laboratory Mouse By the Staff of The Roscoe B Jackson Memorial Laboratory Edited by GEORGE D SNELL 497 pages, 23.5 × 16 cm The Blakiston Co, Philadelphia 1941 Price, \$7.00

The laboratory rat and mouse are the true guinea pigs of science. A contribution to the biology of one can often be applied to the other, so similar are these two species of rodents. Although the biology of the rat was summarized some years ago, we have had to wait until now for an authoritative treatment of the biology of the mouse. The staff of the Jackson Memorial Laboratory is well qualified to make this contribution. The collection of this material from widely scattered articles represents in itself a large piece of work. In addition, however, the authors have worked out many of the problems to which no answer could be found in the literature.

The general investigator will find of most interest the chapters on Embryology, Histology, and Reproduction, as well as those on Parasites and Diseases. The remainder of the book (about one third) deals with genetics and tumor work, as it has been in these fields that mice have been of greatest use.

Each chapter ends with a bibliography giving complete titles and laying before the reader a vast store of information. The emphasis on essentials and the many illustrations and tabulations add greatly to the readability of the book.

E G B

COLLEGE NEWS NOTES

GIFTS TO THE COLLEGE LIBRARY

We gratefully acknowledge receipt of the following gifts donated to the College Library of Publications by Members

Books

- Harry G Armstrong, F A C P, Major (MC), U S Army—"Fit to Fly",
Dr Jacob C Geiger, F A C P, San Francisco, Calif—"1940 Year Book of Public Health" and "1941 Year Book of Public Health",
Dr Franklin H Top (Associate), Detroit, Mich—"Handbook of Communicable Diseases"

Reprints

- Dr M Meredith Baumgartner (Associate), Janesville, Wis —1 reprint,
Dr J Edward Berk (Associate), Philadelphia, Pa —2 reprints,
Dr Edward G Billings, F A C P, Denver, Colo —2 reprints,
Dr William C Boeck, F A C P, Los Angeles, Calif —2 reprints,
Dr Julius P Dworetzky, F A C P, Liberty, N Y —3 reprints,
Dr John A Foley, F A C P, Boston, Mass —1 reprint,
Dr Charles L Hess, F A C P, Bay City, Mich —9 reprints,
Dr Clifton K Himmelsbach (Associate), Lexington, Ky —3 reprints,
Dr Enrique Koppisch, F A C P, San Juan, P R —1 reprint,
Dr Emma S Moss (Associate), New Orleans, La —5 reprints,
Dr Thomas O Nuzum (Associate), Janesville, Wis —1 reprint,
Dr Aaron E Parsonnet, F A C P, Newark, N J —1 reprint,
Dr Harold E Richardson, F A C P, St Paul Minn —1 reprint,
Dr Walter M Simpson, F A C P, Dayton, Ohio —3 reprints,
Dr Elliott P Smart, F A C P, Murphys, Calif —5 reprints,
Dr Ramon M Suarez, F A C P, San Juan, P R —2 reprints,
Ralph M Thompson, F A C P, Major (MC), U S Army —1 reprint,
Charles H A Walton (Associate), Lt Col, R C A M C —3 reprints

A recent contribution to the College Library of Publications by Members is that of a booklet entitled, "Convalescent Care," edited by Dr George Baehr, F A C P, containing the proceedings of a conference on the subject under the auspices of the Committee on Public Health Relations of the New York Academy of Medicine. The book contains the contributions of a very considerable number of College Fellows, including Dr O H Perry Pepper, Philadelphia, Pa, Dr Lewellys F Barker, Baltimore, Md, Dr William S McCann, Rochester, N Y, Dr Russell L Cecil, Dr Howard F Shattuck, Dr Robert L Levy and Dr I Ogden Woodruff, all of New York, N Y.

During November the new and revised 1941 Directory of the American College of Physicians was distributed to all Fellows and Associates of the College in good standing. The late appearance of the Directory was due largely to delays in obtaining paper stock because of defense priorities. The volume of the Directory is greatly increasing each time it is published, now consisting of a cloth bound book of 667 pages, much of which has been condensed in type face in order to restrict weight and volume. One of the new features of the Directory this year is the insertion of a record of all meetings and sessions of the College.

The preparation of a Directory of this character is a task of rather great proportions. Extreme care has been exercised to prevent errors and omissions. Members are urged to advise the Executive Offices of the College of corrections.

Dr Alfred Gordon, F A C P, Philadelphia, appears in the Directory as Consulting Neuropsychiatrist to the Philadelphia State Hospital, which should be corrected to read, "Philadelphia Psychiatric Hospital"

REGIONAL MEETING OF A C P MEMBERS, VIRGINIA

The fall meeting of the Virginia members of the American College of Physicians was held at the Cavalier Hotel, Virginia Beach, Va, on October 7, 1941. In the absence of Dr Henry Mulholland, President, Dr Walter Martin, College Governor for Virginia, presided. The chief guest speaker was Dr James E Paulin, President-Elect of the College, of Atlanta. Officers elected for the coming year were Dr R Finley Gayle, F A C P, Richmond, Va, President, Dr Andrew D Hart, Jr, F A C P, Charlottesville, Va, Secretary.

A C P REGIONAL MEETING PLANNED FOR THE NEW ENGLAND STATES

The Governors of the New England States will hold a regional meeting of the American College of Physicians at Providence, January 14. General arrangements are in charge of the College Governor for Rhode Island, Dr Alex M Burgess, but the General Chairman in charge of the Program is Dr Charles F Gormly, of Providence. Governor Burgess will preside at the scientific session, and Dr Gormly will act as Toastmaster at the special dinner. There will be clinics in the forenoon at the Rhode Island Hospital starting at 10 00 a m. Luncheon will be served at the Hospital at 12 30 and the main scientific session will be held at the Medical Library Auditorium from 2 00 to 5 30 p m. In the evening there will be one of the famous Rhode Island Squantum Club dinners. Dr Roger I Lee, President of the College, and Mr E R Loveland, Executive Secretary, will be among the evening speakers. Invitations have also been issued to other College Officers, but at this time the program cannot be fully announced. College members throughout New England are urged to be in attendance.

REGIONAL MEETING OF NORTH CAROLINA MEMBERS HELD AT CHAPEL HILL

The tenth annual meeting, and the third annual clinical session, of the Fellows and Associates of the American College of Physicians in North Carolina was held at the University of North Carolina School of Medicine, Chapel Hill, October 31-November 1, 1941. Friday afternoon, October 31, was devoted to a symposium on "Ulcerative Lesions of the Colon". The participants in this symposium were

Dr Charles D Thomas (Associate), Sanatorium—"Diagnosis and Management of Tuberculous Ulcerative Colitis",

Dr Opie Norris Smith (Associate), Greensboro—"Concepts as to the Etiology of Non-Specific Ulcerative Colitis",

Dr C Graham Reid (Associate), Charlotte—"Management of Non-Specific Ulcerative Colitis",

Dr Julian M Ruffin, F A C P, Durham—"Amebic Dysentery in North Carolina"

Friday evening there was a dinner meeting at which Dr Charles H Cocke, F A C P, College Governor for North Carolina, presided, and at which Dr William

Allan, Professor of Genetic Medicine, Bowman Gray School of Medicine of Wake Forest College presented an instructive and interesting address on "Hereditary Diseases Which Wreck Childhood" Saturday morning, November 1, the following program was presented

Dr Rufus Henry Temple (Associate), Kinston—"Functional Flatulence and Its Treatment with Prostigmin Bromide";

Dr Thomas W Baker, F A C P, Charlotte—"Coarctation of the Aorta",

Dr Verne B Caviness, F A C P, Raleigh—"Sulphocyanates in Blood Pressure Control",

Dr Mark A Griffin, F A C P, Asheville—"Chronic Alcoholism Its Causation, Treatment and Results",

Dr Frank B Marsh (Associate), Salisbury—"The Plasma Protein Its Physiology Relative to the Normal and Failing Peripheral Circulation"

Sixty-three members of the College attended the meeting, as well as a number of officers of the Medical Corps of the U S Army from Camp Davis and Fort Bragg, who attended the first afternoon session at the invitation of Governor Cocker. The attendance and the enthusiasm of the members were, perhaps, the best of any meeting.

Since the North Carolina members of the College have decided to alternate their annual regional meetings among the three medical schools of the state, their next meeting will be held at the Bowman Gray School of Medicine of Wake Forest College, during October, 1942

DR FRANCIS G BLAKE APPOINTED TO ADVISORY COUNCIL ON MEDICAL EDUCATION

Dr Francis G Blake, F A C P, New Haven, Conn, has been appointed by the President of the College, Dr Roger I Lee, as an official representative of the College on the Advisory Council on Medical Education, taking the place of Dr James H Means, F. A. C. P., Boston, resigned. The American College of Physicians has two appointees on this Council, the other being Dr Hugh J Morgan, F A C P, of Nashville, Tenn. The institutions represented on this Council include the Association of American Medical Colleges, American Hospital Association, Federation of State Medical Boards, Advisory Board for Medical Specialties, American College of Physicians, American College of Surgeons, Association of American Universities, American Association for the Advancement of Science (Division of Medical Sciences), American Protestant Hospital Association, American Public Health Association, Catholic Hospital Association and the National Board of Medical Examiners.

Dr. Henry Bingham Kirkland, F A C P, New York City, will spend most or all of the calendar year 1942 on the staff of the American Hospital in Britain.

Dr Herman S Hoffman (Associate), Washington, D C, has been commissioned a Lieutenant Commander in the U S Naval Reserve as an internist for the George Washington Medical School Unit.

Recently the U S Navy, in addition to its regular organized Reserve, set up an organization called the Volunteer Reserves. The Volunteer Reserves is to be composed of experts and specialists in the various fields. In the medical division it will consist chiefly of units to be established in various universities composed of men chosen by the university. Each unit will consist of nine specialists—Surgeon, Internist, Orthopedic Surgeon, Otolaryngologist, Urologist, Dentist, etc. The Surgeon and Internist will be considered the principal members of the unit. It is set forth by the

regulations that the members of the units will not be called to active duty as individuals, but only with the entire unit. It is understood further that these units are not to be called to active duty except in case of urgent need, interpreted as actual war or grave national emergency, to be used in base hospitals and on hospital ships

On October 7, 1941, Dr. Bernard I. Comroe, F A C P, Philadelphia, Pa., addressed the Camden County (N J) Medical Society on "Practical Pointers in the Treatment of Arthritis"

During September, 1941, Dr. Heibert T. Kelly, F A C P, Philadelphia, Pa., presented a paper on "The Modern Science of Nutrition in Health and Disease," with a motion picture in technicolor, at the Pennsylvania Meeting on Nutrition and Consumer Problems for Defense in Harrisburg.

Dr. Kelly also presented a paper on "The Significance of the Oral Mucosa and Teeth in Deficiency Disease" at a meeting of the Academy of Stomatology, October 28, 1941, at Philadelphia, Pa.

Dr. Ross M. Lymburner, F A C P, Hamilton, Ont., Canada, was the guest speaker at the Scientific Meeting of the Brant County Medical Society, October 23, 1941, in Paris, Ont. His subject was "The Diagnosis of Certain Types of Anemia with Fundamentals of Treatment"

On September 1, 1941, Dr. Frank S. Horvath, F A C P, was promoted to the position of Professor of Clinical Medicine at the Medical School of Georgetown University, Washington, D C.

Dr. August A. Wernei, F A C P, St. Louis, Mo., addressed the Shreveport (La.) and Fourth District Medical Societies, October 7, 1941, on "The Effect of the Ductless Glands on Growth and Development"

Dr. Baldwin L. Keyes, F A C P, Philadelphia, Pa., has been advanced from Clinical Professor of Psychiatry to Professor of Psychiatry at the Jefferson Medical College of Philadelphia, effective October 1, 1941.

Dr. Nathan W. Chaikin (Associate), New York, N Y., has recently been assigned as voluntary assistant pathologist to the Metropolitan Hospital, under the supervision of Dr. Andrea Saccone, Director of the Laboratory and Associate Professor of Pathology of the New York Medical College. Dr. Chaikin, since July, 1941, has been studying, under the auspices of the New York Medical College, the microscopic and gross pathological material and autopsies as encountered on the medical and surgical services.

The Medical Society of the State of Pennsylvania will hold its 1942 annual meeting in Pittsburgh, Pa., October 5-8.

The Illinois State Medical Society conducted a postgraduate conference in the Eighth Councilor District at Danville, November 6, 1941. Among the speakers were

Dr. John R. Vonachen, F A C P, Peoria, Ill.—"Present Status of Vitamin Therapy",

Dr. M. Herbert Barker, F A C P, Chicago, Ill — "Nephritis",
 Dr. Lee C. Gatewood, F A C P, Chicago, Ill — "Medical Management of Upper Gastrointestinal Tract Ulcer",
 Dr. Robert S. Berghoff, F A C P, Chicago, Ill, conducted a heart clinic

Dr. Harold W. Jones, F A C P, Philadelphia, Pa, addressed the Essex County (N J) Medical Society, Newark, October 9, 1941, on "Value of Blood and Plasma in Transfusion"

At a meeting of the Morris County (N J) Medical Society, Morris Plains, on October 16, 1941, Dr. Hugo Roesler, F A C P, Philadelphia, Pa, spoke on "Bedside Diagnosis and Treatment of Disturbances of Rate and Rhythm"

Dr. Milton B. Plotz, F A C P, Dr. Burton L. Zohman, F A C P, and Dr. Charles G. Williamson (Associate) have been promoted to Assistant Clinical Professors of Medicine at the Long Island College of Medicine, Brooklyn, N Y.

The Southern Illinois Medical Association held its 67th Annual Meeting in Murphysboro, November 6, 1941. Among those who participated in the program were.

Dr. Ralph A. Kinsella, F A C P, St. Louis, Mo — "Medical Management of Nephritis",

Dr. James H. Hutton, F A C P, Chicago, Ill — "Endocrine Therapy Including That of the Menopause",

Dr. Carl G. Morlock, F A C P, Rochester, Minn — "Problems of the Small Ulcerating Gastric Lesion"

At a meeting of the North Side Branch of the Chicago Medical Society, October 16, 1941, Dr. Virgil P. Sydenstricker, F A C P, Augusta, Ga, discussed "Vitamin Deficiencies"

On October 29, 1941, Dr. John A. Toomey, F A C P, Cleveland, Ohio, presented a paper on "Infantile Paralysis" at the 16th Annual Clinic of the Highland Park (Mich.) Physicians' Club

The University of Rochester School of Medicine and Dentistry and the Medical Society of the County of Monroe cooperated with the Medical Society of the State of New York in conducting a Postgraduate Institute in Rochester, N Y, November 11-13, 1941. Dr. Russell L. Haden, F A C P, Cleveland, Ohio, conducted a forum on "Laboratory Methods in Clinical Medicine"

At one of the evening sessions Dr. John A. Toomey, F A C P, Cleveland, Ohio, presented the Monroe County Medical Society Lecture on "Polio-myelitis"

One of the series of "Lectures to the Laity" sponsored by the Brooklyn Institute of Arts and Sciences, the Medical Society of the County of Kings and the Academy of Medicine of Brooklyn will be presented on March 24, 1942, by Dr. Walter C.

Alvarez, F A C P, Senior Consultant in Medicine, Mayo Clinic, Rochester, Minn
Dr Alvarez will discuss "Food, Faith and Civilization"

The Central Society for Clinical Research held its 14th Annual Meeting in Chicago, Ill, November 7-8, 1941 Among the speakers were

Dr Alvin E Price, F A C P, Detroit, Mich—"Sputum Studies in Pneumonia The Selection of Therapy",

Dr Elmer L Sevringhaus, F A C P, Madison, Wis—"Treatment of Parathyroid Tetany",

Dr George E Wakerlin, F A C P, Chicago, Ill—"Treatment of Experimental Renal Hypertension with Renin",

Dr Nathan S Davis, III, F A C P, Chicago, Ill—"Chronic Sub-Nutrition and Essential Hypertension"

A group of thirty-seven interns, representing fifteen nations of South, Central and Caribbean America, have arrived in the United States to spend a year in United States hospitals and medical schools These interns have received fellowships for study in this country through the cooperation of the Office of the Coordinator of Inter-American Affairs, the Pan American Sanitary Bureau and other participating institutions Fellows of the College who are among the members of the committee of sponsors for the plan under which these interns are studying are the following

Dr Walter W Palmer, Bard Professor of Medicine, Columbia University College of Physicians and Surgeons, New York, N Y,

Dr Currier McEwen, Dean and Associate Professor of Medicine, New York University College of Medicine, New York, N Y,

Dr William S McCann, Charles A Dewey Professor of Medicine, University of Rochester School of Medicine and Dentistry, Rochester, N Y,

Dr William J Kerr, Professor of Medicine, University of California Medical School, San Francisco, Calif,

Dr Francis G Blake, Dean, Yale University School of Medicine, New Haven, Conn,

Dr William D Cutter, Secretary, Council on Medical Education and Hospitals, American Medical Association, Chicago, Ill

The Southern Medical Association held its 35th Annual Meeting in St Louis, Mo, November 10-13, 1941 Dr James S McLester, F A C P, Birmingham, Ala, addressed a Public Session, Monday evening, November 10, on "Nutrition in War Time" On Tuesday evening, November 11, which was President's Night, Dr Paul H Ringer, F A C P, President of the Association, Asheville, N C, delivered an address on "Giants of Yesterday"

Dr James S McLester, F A C P, Birmingham, Ala, spoke on "Functional Disorders of the Digestive Tract," and Dr Philip S Hench, F A C P, Rochester, Minn, spoke on "Management of Chronic Arthritis," at the 6th Annual Meeting of the Gulf Coast Clinical Society, held in Pensacola, Fla, October 16, 1941

Dr Luther Bach (Associate), Newport, Ky, has been chosen one of the Vice Presidents of the Kentucky State Medical Association

At the recent annual meeting of the Michigan State Medical Society in Grand Rapids, Dr Henry R Carstens, F A C P, College Governor for Michigan, Detroit, was inducted into the Presidency

Dr. Eugene F Du Bois, F A C P, New York, N Y, was honored at a dinner October 9, 1941, at the Waldorf-Astoria, to mark his retirement as Physician-in-Chief of the New York Hospital and Professor of Medicine at Cornell University Medical College Dr Du Bois has been connected with Cornell University Medical College since 1910 Since 1930 he has been Professor of Medicine, and since 1932, Physician-in-Chief of the New York Hospital He will continue as Professor of Physiology and Head of the Department of Physiology and Biophysics at the Medical School

On September 11, 1941, the Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N C, was formally opened Dr Thurman D Kitchin, F A C P, President of the College, presided at the opening exercises and Dr Thomas T Mackie, F A C P, New York, N Y, spoke on "The Challenge of a New Medical School to the Faculty, Students and Community"

Wake Forest College School of Medical Sciences, which offered only the first two years in medical training, announced in 1939 that it would move to Winston-Salem and expand into a four year school The expansion was made possible by a gift from the Bowman Gray Fund, from the late Mr Gray of Winston-Salem

Dr Coy C Carpenter, F A C P, who was Dean of the two year school of Wake Forest will continue as Dean of the Bowman Gray School of Medicine

The Saranac Lake Medical Society and the Osler Club, Saranac Lake, N Y, have announced the following winter program of lectures

January 28, 1942, "Newer Chemotherapeutic Methods"—Dr Norman J Plummer, F A C P, New York, N Y,

February 4, 1942, "Hematologic Aspects of Tuberculosis of the Spleen and Lymph Nodes"—Dr William P Thompson, F A C P, New York, N Y,

February 11, 1942, "Gabriels Sanatorium Evening"—Dr John N Hayes, F A C P, Saranac Lake, N Y, in charge,

March 4, 1942, "Stonywold Sanatorium Evening"—Dr Wayne L Henning (Associate), Lake Kushaqua, N Y, in charge,

March 18, 1942, "Practical Problems of Peptic Ulcer"—Dr Sara M Jordan, F A C P, Boston Mass

At the annual meeting of the Pennsylvania Psychiatric Society in Philadelphia, October 9, 1941, Dr Baldwin L Keyes, F A C P, Professor of Psychiatry at the Jefferson Medical College of Philadelphia, was inducted into the Presidency Dr George J Wright, F A C P, Professor of Neurology at the University of Pittsburgh School of Medicine was chosen President-Elect

Dr Russell L Cecil, F A C P, Professor of Clinical Medicine at Cornell University Medical College was one of the speakers at the 10th Annual Postgraduate Medical Assembly of South Texas, held in Houston, December 4 1941

OBITUARIES

DR EDWARD EVERETT CAMPBELL

Dr Edward Everett Campbell, F A C P , of Columbus, Ohio, died on July 4, 1941, as a result of an automobile accident which occurred while he was making a professional call

Dr Campbell was born in Logan, Ohio, November 23, 1883. He attended the local schools and was graduated from the Starling Medical School of Columbus in 1907. For many years he enjoyed a large general practice in Logan, Ohio. He then became interested in internal medicine and took a postgraduate course at Harvard Medical School and also studied Cardiology in London, England.

He then moved to Columbus, Ohio, where he devoted his entire time to the practice of Internal Medicine. He was a member of the Senior Staff of Grant and Mount Carmel Hospitals of Columbus. He was also a member of the Courtesy Staff of The Starling-Loving University Hospital. Dr Campbell was a member of the Columbus Academy of Medicine, Ohio State Medical Society, American Medical Association, American Heart Association, and Fellow of The American College of Physicians since 1936. He was an author of several published papers.

Dr Campbell, to those who knew him well, was a fine friend, a marvelous host, and a man who really enjoyed life. He took great pride in upholding the standard of the American College of Physicians and gave of his full strength to his patients. The College has lost an ardent Fellow, his patients a fine doctor, and his friends a loyal and steadfast companion.

A B BROWER, M D , F A C P ,
Governor for Ohio

DR CLEMENT L JONES

Dr Clement L. Jones, F A C P , of Springfield, Ohio, died August 2, 1941, from a coronary accident. Dr Jones was born in Winchester, Indiana, on April 29, 1876, the son of Dr. and Mrs. Levi Miller Jones, and there he received his early education. He attended Washington and Jefferson College and received the Degree of Bachelor of Science in 1899. In 1903 he was graduated from the Johns Hopkins University School of Medicine, and in 1904 he received the degree of Master of Science from Washington and Jefferson College.

After leaving Johns Hopkins he served as pathologist to a hospital in Vicksburg, Miss., and soon was made an Assistant in Medicine at Starling Medical College in Columbus, Ohio. Dr Jones was Pathologist at Mount Carmel Hospital in Columbus from 1904 to 1906, and was for many years pathologist at Rickly Memorial Hospital in Springfield, Ohio. He practiced medicine in Springfield for thirty years.

For many years he was a member of the Staff of the City Hospital in Springfield. At his death he was Director of the Department of Medicine of that hospital, and its Cardiologist. He conducted cardiac clinics twice weekly and this service was a source of great pride and satisfaction to him. He was Director of the Springfield Clinical and Pathological Laboratory since 1913.

Dr. Jones served his country with great distinction during the World War. He was formerly Secretary and President of the Clark County Medical Society. He was a member of the Clark County Medical Society, the Ohio State Medical Association, the American Medical Association, the American Heart Association, and The American College of Physicians. He was also a Diplomate of The American Board of Internal Medicine.

Dr. Jones never lacked enthusiasm for his work and constantly sought to keep abreast of the times in all things medical. He was a true friend and a gracious gentleman. The profession and people of Springfield have lost a fine doctor in the passing of Dr. Jones.

A. B. BROWER, M.D., F.A.C.P.,
Governor for Ohio

DR. GEORGE FORDHAM

Dr. George Fordham, F.A.C.P., Medical Supervisor of the Powellton Division of the Koppers Coal Company, died unexpectedly of a heart ailment at his Powellton, West Virginia, home on October 4, 1941, at the age of 63 years. He was born March 4, 1878, in New York City, graduated in pharmacy from the New York College of Pharmacy in 1897, and received his medical degree from the University of Virginia, Department of Medicine, in 1907. Dr. Fordham did postgraduate work at Harvard and the Massachusetts Institute of Technology.

The deceased served as a private in the United States Army during the Spanish American War. In 1917 he was commissioned as a Captain in the Army Medical Corps, and advanced to Lieutenant Colonel in 1919. He served in the American Expeditionary Force in France and was cited by General Headquarters. He also received the silver medal of the Polish Red Cross in 1921, having seen active service with the Polish Army during the defense and retreat from Kiev that year.

During recent years he has been a Member of the Staff at Morris Memorial Hospital for Crippled Children (Milton); Consultant, Dust Investigation U. S. Public Health Service; Member and former President, Fayette County Medical Society and Society of Industrial Physicians and Surgeons of West Virginia; Member, West Virginia State Medical Association, Association of Industrial Physicians and Surgeons, Association of Military Surgeons, Southern Medical Association and National Safety Council; Fel-

low, American Medical Association and American College of Physicians (1938), author of many published papers

During his service in Poland, Dr Fordham married an American Red Cross nurse, Miss Mary Frances Yodzis, who survives. Also surviving is one son, George Fordham, Jr., a medical student at Duke University.

Dr Fordham was buried with full military honors in Arlington National Cemetery.

ALBERT H. HOGE, M.D., F.A.C.P.,
Governor for West Virginia

DR. GEORGE MACDONALD ALBEE

Maintaining, even to his last hours, his sincere and studied interest in cardiac disease, Dr. George Macdonald Albee died at his home in Worcester, Mass., August 10, 1941. Truly did he "die in the harness"—active to the very end, according to his oft expressed desire. For some weeks he had been made uncomfortable by increasing symptoms of coronary insufficiency, progressing finally to a terminal coronary thrombosis.

He was born in Hopkinton, Mass., in 1871, to parents of old New England lineage. His father, Dr. George Sumner Albee, had been a country practitioner in Hopkinton for many years. After receiving his medical degree in 1893 from New York University Medical College, Dr. Albee practiced a year in Stowe, Vt., and then established his office in Worcester, Mass., for the general practice of medicine.

Following this country's entrance into the first World War, Dr. Albee promptly offered his services to the government, and was ordered to Camp Dix as a Captain in the Medical Corps of the U. S. Army. Here his immediate problem was the historic influenza epidemic of 1918. From Camp Dix he attended a course at the Army Heart Hospital in Lakewood, N. J., and then became Chief of the Cardiovascular Board at Camp Custer, and later at Camp Meade. He received his honorable discharge from the Army in July, 1919.

Before returning to Worcester, he took postgraduate work in the field of cardiac disease at Johns Hopkins Hospital, Baltimore, Peter Bent Brigham Hospital, Boston, The Mayo Clinic, Rochester, and the National Heart Hospital, London. Following this concentration in a subject which was always his most vital interest, he returned to practice in Worcester, where he has ever since been fondly known as "the heart doctor."

He was a member of the Massachusetts Medical Society, a Fellow of the American Medical Association, and a Fellow of the American College of Physicians since 1926. He belonged to the Johns Hopkins Alumni Association and to the New England and American Heart Associations. In 1937 he was certified as a specialist by the American Board of Internal Medicine. Although Dr. Albee, by reason of a somewhat retiring nature,

consistently avoided selection to office in the various local medical societies, he was made a governor of the New England Heart Association the year before his death—an honor which he deeply appreciated. Locally he was a member of the Worcester Club, Tatnuck Country Club, Bohemian Club, Practitioners' Club, Gen Devens Post of the American Legion and the Military Order of the World War.

Dr. Albee might well be called the dean of cardiology in Worcester. In his long association with the Worcester City Hospital as its Cardiologist, one may call to mind his tender and knowing ministrations to the old-fashioned and temperamental electrocardiograph which at one time filled a whole hospital room in its complicated expanse, or one may recall his quick and shrewd estimate of a person's cardiac status, which he could in turn aptly express to the patient by the use of some telling and appropriate aphorism. He indeed filled a big niche in the hospital staff. At the age of sixty-two he suggested that he be "promoted to the consulting staff" and not simply retired—a method of expression which has become standard parlance, when once a staff member reaches that venerable age.

Besides the Worcester City Hospital, Dr. Albee, at the time of his death, was Consulting Cardiologist to Fairlawn, Belmont, Henry Heywood Memorial (Gardner) and Webster District Hospitals, and Hospital Cottages for Children (Baldwinsville).

Dr. Albee eagerly and regularly attended the various conventions of the American College of Physicians and the American Medical Association, as well as the local meetings of the New England Heart Association and the Worcester District Medical Society. He was easy to approach and affable. His practical and working knowledge of cardiology was very effective. This, together with a unique and delightful personality, gave to Dr. Albee a position supreme in professional circles and made him well loved by Worcester's everyday citizenry.

F. BENJAMIN CARR, M.D., F.A.C.P.,

Worcester, Massachusetts

DR. LOUIS FAUGERES BISHOP, SR.

Dr. Louis Faugeres Bishop, Sr., M.A., M.D., Sc.D., F.A.C.P., was born in New Brunswick, N.J., March 14, 1864, and passed away October 6, 1941, of pneumonia, at his home, 1172 Park Avenue, New York, N.Y.

Dr. Bishop received a liberal education in the schools of his native city. He was a graduate of St. Paul's School, Concord, N.H. He graduated from Rutgers College, B.A., in 1885, and received the honorary degrees of M.A. in 1889 and Sc.D. in 1920 from the same institution. He studied medicine with Dr. William Elmer of Trenton, N.J. In 1886 he entered the College of Physicians and Surgeons of Columbia University, and received his M.D. degree in 1890, thereafter becoming Resident Physician at

St Luke's Hospital, New York City, 1889-1892 Thereafter he was identified for three months with the Sloan Maternity Hospital, and for five years held an appointment at the Vanderbilt Clinic Beginning in 1895 he engaged in private practice in New York City, and in 1908 devoted himself exclusively to diseases of the heart and blood vessels Dr Bishop was formerly Professor of Diseases of the Heart and Circulation at Fordham University School of Medicine, a former President of the Good Samaritan Dispensary, former Consulting Physician to Mercy Hospital (Hempstead, L I, N Y), and at the time of his death he was Consultant in Diseases of the Heart, Lincoln Hospital, and Consulting Cardiologist to the Sea View (Staten Island) and Goshen Hospitals

During the World War, he served as Cardiologist on local Advisory Board No 23, May 3, 1918, through March 31, 1919 He was a member and former secretary (1895-1903) and two years Chairman of the Section on Medicine of the New York Academy of Medicine, member of the New York Pathological Society, Society of Alumni of St Luke's Hospital, American Society of Tropical Medicine, American Therapeutic Society, American Medical Editors and Authors Society, New York State and New York County Medical Societies, New York Gastro-enterological Association, Society of Medical Jurisprudence, New York Society for the Relief of Widows and Orphans of Medical Men, and American Heart Association, Fellow of the American Medical Association He was a Director of the New York School for the Deaf, Director of the Y M C A of New York City, Trustee of Rutgers University, Trustee of the Museum of the American Indian, New York City, a member of the Sons of the Revolution, Founders and Patriots of America, Pilgrims, Holland Society, St Nicholas Society, New York Genealogical and Biographical Society, a member of the following clubs University, Metropolitan, Racquet and Tennis, Seawanhaka Corinthian Yacht, New York Athletic, Columbia University, Explorers Club, Maidstone Club, East Hampton (L I, N Y) Fencers Club and the Rotary Club of New York

Dr Bishop was author of a host of publications, starting in 1893 with an article dealing with "A New Measurement in the Study of Fever" He published one or more articles annually almost to the end of his career Among books published by him were "Blood Pressure" (with four revisions, from 1904 to 1914), "Arterial Sclerosis" (1914, with two revisions thereafter), "Heart Troubles, Their Prevention and Relief" (1920), "A Key to the Electrocardiogram" (1923), "History of Cardiology" (1927), "The Mechanism of the Heart and Its Anomalies" (a translation from the French of Emile Geraudel, 1930)

Dr Bishop was a Charter Fellow of the American College of Physicians, and played a large part in its founding in 1915 and in its early administration His name appears on the first roster of physicians declared Fellows of the College "in recognition of their special meritorious services to the

science and practice of medicine" His participation in College affairs covered many years, and he was deeply interested in all of its activities to the end of his life

Dr Bishop is survived by his wife, Mrs Charlotte Dater Bishop, one son, Louis Faugeres Bishop, Jr , M D , F A C P , a daughter-in-law, Mrs Kathleen Sinclair Bishop, and four grandchildren

C F TENNEY, M D , F A C P ,
Governor for Eastern New York

DR LOUIS LAWRENCE SYMAN

Dr Louis L Syman, F A C P , was born in Cleveland, Ohio, in 1871 He pursued his elementary education in Cleveland and was graduated from Wittenberg College with A B and A M degrees He received his medical certificate from Starling Medical College in Columbus in 1898 He was Staff Physician at the Springfield City Hospital from 1898 to 1925 During the Spanish-American War he was Recruiting Examiner During the World War he was a Regimental Surgeon and also Surgeon of the R O T C of Wittenberg College

He was a member of the Clark County Medical Society, the Ohio State Medical Society and the American Medical Association He had been a Fellow of the American College of Physicians since February 25, 1920 He retired from the practice of medicine a number of years ago because of physical disability

A B BROWER, M D , F A C P ,
Governor for Ohio

DR WILLIAM HENRY RILEY

Dr William Henry Riley died August 24, 1941, at the home of his son, William H Riley, Jr , near Mattoax, Va , after a brief illness For nearly fifty years he was chief neurologist at the Battle Creek Sanitarium He was born in Boston, February 5, 1860, and early came to Michigan He was graduated with a B A degree from Battle Creek College and with a medical degree from the University of Michigan in 1886, when he returned as a member of the staff at the Sanitarium A few years later he was appointed Medical Director of the new Boulder (Colorado) Sanitarium which post he held for eight years While there he was part-time professor of neurology in the medical department of the University of Colorado He was married December 23, 1897, to Miss Henrietta M Zollinger, a graduate of the University of Wisconsin

On returning to Battle Creek he was appointed professor of neurology in the American Medical Missionary College, which position he held with distinction until the College was merged with a Chicago university in 1914.

In 1912 he spent some months in leading clinics in Munich, Vienna, Dublin and London. He was a Fellow of the American College of Physicians (1923), the American Medical Association, the American Psychiatric Association, and the Society for Research in Mental and Nervous Diseases.

Dr. Riley was a keen student, with an unusually clear, scientific mind. He made many obscure diagnoses and was an outstanding scientific figure in any gathering which he attended. His scientific papers and productions were many. He was a modest, conscientious man, devoted to his patients, and he will long be remembered for his faithful, untiring service to them.

Dr. Riley is survived by his widow, a son, and a sister, Miss Minnie Riley, R. N.

A. B. OLSEN, M. D., F. A. C. P.

DR. JOSEPH WIENER

Dr. Joseph Wiener died suddenly at his home in Asbury Park, N. J., September 8, 1941, of a coronary thrombosis. Though only forty years of age, Dr. Wiener had established a definite place for himself in his community. He was a 32d degree Mason and a man of wide cultural interests, being especially interested in photography and music. He was beloved by his patients, had the full confidence of his professional associates, and his untimely death cuts short a career which gave promise of great usefulness both as a citizen and as a physician.

Dr. Wiener was born in New York City, October 19, 1901, attended the University of Maryland, where he first took a premedical course, and was then graduated in medicine in 1925. He interned, 1925 to 1927, at the Chestnut Hill Hospital, Philadelphia, and the Ford Hospital, Detroit. In 1927 he took up practice in Asbury Park and received an appointment in the medical O. P. D. of the Pennsylvania Hospital (Philadelphia), which he held for seven years. Also in 1927 he became Attending physician at the Monmouth Memorial Hospital (Long Branch), and the following year was placed in charge of its Cardiac Clinic. In 1933 he was appointed an Assistant Physician, Vascular Clinic, New York Post-Graduate Medical School and Hospital, and recently was made Chief Cardiologist at the Fitkin Memorial (Neptune, N. J.).

He was a member of the Monmouth County Medical Society, the Medical Society of New Jersey, the American Therapeutic Society, and was a Fellow of the American Medical Association. He became a Fellow of the American College of Physicians, December 13, 1936.

Dr. Wiener is survived by a son, Joseph, junior, aged eleven, a brother, Murray, of Washington, D. C., and a sister, Mrs. Max Warner, of Bradley Beach, N. J.

GEORGE H. LATHROPE, M. D., F. A. C. P.,
Governor for New Jersey

POSTGRADUATE FACILITIES IN INTERNAL MEDICINE AND ALLIED SUBJECTS

The Board of Regents of the American College of Physicians has directed the publication in the "Annals of Internal Medicine," from time to time, of announcements relating to available educational opportunities in Internal Medicine and the allied specialties, particularly from the standpoint of postgraduate courses

An attempt has been made, by communicating with the deans of all medical schools in the United States and Canada and with organized postgraduate meetings and societies, to collect all available data. Unfortunately the Executive Office has been unable to obtain replies from all these agencies, and, in some instances, when replies have been forwarded the information is somewhat incomplete. The following announcement of postgraduate courses and postgraduate meetings, therefore, will be supplemented in future reports. For greater detail, consult the institutions

Part I—Graduate Institutions

Columbia University
New York Post-Graduate Medical School and Hospital
Irving S. Wright, M.D., Executive Officer
303 E. 20th St.
New York, N. Y.

A number of full-time and part-time courses designed to help the physician to keep abreast of modern procedures in the diagnosis and treatment of diseases are offered throughout the year

Full-time Courses

300—Seminar in Internal Medicine

Two months, beginning January 5, 1942, and April 6, 1942. Registration may be accepted for one month, but preference is given to those who enroll for both months. Fees, \$125.00 for one month, \$200.00 for two months

330—Arthritis and Rheumatic Diseases

Five days, March 2-6, 1942, Fee, \$35.00

331—Allergy

Three weeks, December 1-19, 1941, and April 13-May 1, 1942, Fee, \$150.00

332—Cardiovascular Diseases

Three weeks, June, 1942. Exact dates not announced; Fee, \$75.00

333—Acute and Chronic Diseases of the Chest

Ten days, February 2-13, 1942; Fee, \$50.00

337—Diabetes Mellitus, Nephritis, and Hypertension

Five days, March 9-13, 1942, Fee, \$35.00

338—Therapeutics

Five days, December 1-5, 1941, Fee, \$35.00

341—Symposium in Medicine

Ten days, June, 1942, exact dates not announced. Registration will be accepted for the entire ten days or for either the first or second five-day session. Fees: \$30.00 for five days; \$50.00 for ten days

- 345—*Electrocardiography*
Five days, May 18-22, 1942, Fee, \$50 00
- 347—*Clinical Interpretations of Laboratory Data*
Five days, June, 1942, exact dates not announced, Fee, \$35 00
- 348—*Tropical Medicine*
Five days, May 25-29, 1942, Fee, \$50 00
- 350—*Pulmonary Tuberculosis*
Two weeks, May 4-16, 1942, Fee, \$50 00
- 351—*Symposium on the Clinical Applications of Chemotherapy and Vitamins*
Five days, February 16-20, 1942, Fee, \$35 00
- 353—*Metabolism, Including Endocrinology and Nutrition*
Five days, May 11-15, 1942, Fee, \$35 00
- 1110—*Diseases of the Liver and Biliary Tract*
Six days, June, 1942, exact dates not announced, Fee, \$35 00
- 1134—*Endocrinology*
Ten days, March 16-27, 1942, Fee, \$50 00
- 1140—*Peripheral Vascular Diseases*
Five days, December 8-12, 1941, Fee, \$35 00
- 1142—*Recent Developments in Diagnostic Procedures*
Ten days, January 19-30, 1942, Fee, \$50 00
- 1143—*Physical Therapy*
Five days, April 6-10, 1942, Fee, \$35 00

Part-time Courses

The following courses will be offered beginning the week of January 5, 1942, and April 6, 1942. The courses consist of lectures and clinical demonstrations stressing the diagnosis and treatment of the various disease conditions.

- 301—*Arthritis and Rheumatic Diseases*
Two months, 9 00 a m to 12 00 m, Tuesdays, Fee \$35 00
- 303—*Cardiology*
Two months, 2 00 to 5 00 p m, Mondays, Fee, \$35 00
- 304—*Clinical Interpretations of Laboratory Data*
Two months, 9 00 to 11 00 a m, Wednesdays, Fee, \$25 00
- 307—*Problems in Diagnosis*
Two months, 9 00 a m to 12 00 m, Mondays, Fee, \$35 00
- 308—*Acute and Chronic Diseases of the Chest*
Two months, 9 00 a m to 12 00 m, Thursdays, Fee, \$35 00
- 309—*Diseases of the Thyroid and Other Endocrine Glands, and Nutrition*
Two months, 9 00 a m to 12 00 m, Fridays, Fee, \$35 00
- 310—*Diseases of the Liver and Biliary Tract*
Two months, 11 00 a m to 1 00 p m, Wednesdays, Fee, \$25 00
- 311—*Gastroenterology*
Two months, 2 00 to 5 00 p m, Wednesdays, Fee, \$35 00

312—*Diseases of the Spleen and Clinical Hematology*

Two months, 2 00 to 4 00 p m, Fridays, Fee, \$25 00

315—*Psychological Aspects of Internal Medicine*

Two months, 4 00 to 5 00 p m, Fridays; Fee, \$15 00

319—*Peripheral Vascular Diseases*

Two months, 2 00 to 4 00 p m, Tuesdays, Fee, \$25 00

320—*Gastroscopy*

Three hours weekly for twelve weeks, 9 00 a m to 12 m, Wednesdays, May 6–July 22, 1942, Fee, \$75 00

335—*Electrocardiography*

Two two-hour sessions weekly for four weeks, 9 00 to 11 00 a m, Tuesdays and Thursdays, April 7–30, 1942, Fee, \$50 00

344—*Advanced Electrocardiography*

Two two-hour sessions weekly for four weeks, 9 00 to 11 00 a m, Tuesdays and Thursdays, May 5–28, 1942, Fee, \$50 00

The New York Post-Graduate Medical School has also scheduled similar courses in neurology and psychiatry, pathology, pediatrics, bacteriology, dermatology and syphilology

Cook County Graduate School of Medicine

James F Askin, Registrar

427 S Honore St

Chicago, Ill

Electrocardiography and Heart Disease—Monthly Course, starting first day of each month, except August Fee, by arrangement

Röntgenology—Starts every Monday

Courses in roentgen-ray diagnosis, fluoroscopy and therapy. Fee, by arrangement

University of Minnesota

The Mayo Foundation

Donald C Balfour, M D, Director

Rochester, Minn

The Graduate School of the University of Minnesota in cooperation with the Mayo Foundation offers full-time courses in the basic sciences and clinical specialties leading to the degree of Master of Science or Doctor of Philosophy For the Master's degree in clinical subjects, two or three years are required; for the Master's degree without special designation in the laboratory sciences a minimum of one year (three quarters) of residence is required, for the Master's degree with the field named, such as M S in Path three years are required Fee, \$75 00 per quarter for residents of Minnesota \$125 00 per quarter for non-residents

A limited number of fellowships and assistantships in the various branches of medicine and surgery are offered at the Mayo Foundation under the auspices of the University of Minnesota These fellowships and assistantships are designed for those who have recently completed their internship following graduation from medical school

Throughout the year short periods of lectures demonstrations, etc, are arranged at the Mayo Foundation These symposia are devoted to a specific subject or field, and give a more comprehensive presentation of material of variable scope Dates and subjects of the symposia are not announced

University of Pennsylvania Graduate School of Medicine
 Robin C. Buckle, M.D., Dean
 36th & Pine Sts
 Philadelphia, Pa

This institution offers the following opportunities in advanced medical studies to physicians

Organized Basic University Intramural Graduate Studies in each of the clinical specialties leading to a certificate Internal Medicine, Pediatrics, Neurology-Psychiatry, Dermatology-Syphilology, Radiology—eight months, October–June, 1942

University-aegis Graduate Intramural or Extramural Cooperative Continuation Clinical and Thesis Studies in each of the above special clinical fields, or in an approved division thereof, require an additional two or more years of training and lead to the degree of Master of Medical Science. The University does not provide these studies but does cooperate therewith.

Individual Graduate Intramural or Extramural Cooperative or Independent further Continuation Research Studies in the field related to the previously attained Master's degree, which requires an additional one or two years, and leads to the degree of Doctor of Medical Science. These studies are specially authorized and recognized by the University for each doctorate degree, but are not usually provided for.

Specially Planned Intramural or, partially, Extramural Graduate Nonclinical Candidacies in the Medical Sciences require three or more years and lead to the degree of Doctor of Medical Science. These candidacies are usually based on departmental voluntary assistantships, as such posts become available.

The Graduate School of Medicine of the University of Pennsylvania also sponsors personal courses in subdepartmental fields. During the 1941–42 session the following courses in the Department of Internal Medicine will be offered:

Cardiology—William D. Stroud, M.D., Professor of Cardiology

Eight Thursdays, 48 hours, beginning the first Thursday of January and April, 1942, Fee, \$80.00

Electrocardiography and Cardiac Roentgenology—Thomas M. McMillan, M.D., Associate Professor of Cardiology, and Samuel Bellet, M.D., Instructor in Cardiology

Five days, 30 hours, dates by special arrangement, Fee, \$60.00

Clinical Gastro-enterology—Henry L. Bockus, M.D., Professor of Gastro-enterology

Sixteen weeks, 500 hours, dates by special arrangement, Fee, \$400.00

Allergy—Harry B. Wilmer, M.D., Associate Professor of Allergy

Four weeks, 40 hours, dates by special arrangement, Fee, \$150.00

Diabetes Mellitus—Edward S. Dillon, M.D., Assistant Professor of Diseases of Metabolism

Two to four weeks, 75 hours, dates by special arrangement, Fee, \$150.00

Part II—Other Medical Colleges

Boston University School of Medicine

Bennett F. Avery, M.D., Dean

80 E. Concord St.

Boston, Mass.

This institution offers the following short courses:

Diagnosis and Treatment of Digestive Diseases

Two weeks, July 6–18, 1942, Fee, \$75.00

Cardiology and Electrocardiography

Two weeks, July 20–August 1, 1942, Fee, \$75 00

College of Medical Evangelists

Walter E Macpherson, M D , Associate Dean

Boyle & Michigan Aves

Los Angeles, Calif

Postgraduate extension courses are conducted under the auspices of the Committee on Postgraduate Medical Education of the Faculty of the Los Angeles Division of the Medical School in cooperation with the Committee on Medical Education of the Alumni Association of the College. The courses will be conducted on the basis of one class or clinical period each week and will consist of didactic lectures, round table discussions, clinics and demonstrations. The following courses will be offered during the winter quarter, January 4–March 27, 1942

General Medicine

Twelve hours, Fee, \$25 00

Cardiology

Thirty hours, Fee, \$50 00

Neurology

Ten hours, Fee, \$20 00

Columbia University College of Physicians and Surgeons

Willard C Rappleye, M D , Dean

630 W 168th St.

New York, N Y.

Throughout the year this institution in cooperation with certain of the leading hospitals in New York City offers courses for continuation training and advanced experience in the clinical fields of medicine. Courses are divided into two groups—those for the general practitioner and those for the specialist. Courses for the general practitioner are designed to present the latest advances in the various fields of medicine with emphasis on diagnosis and treatment, rather than theoretical considerations. Much of the instruction is carried out in small groups at the bedside and in the outpatient clinic. Courses for the specialist in subjects of interest and value are provided in several fields of medicine. The program of these courses is necessarily flexible and registration is limited to those specialists who have had adequate preliminary training and experience.

Courses for General Practitioners

Clinical Cardiology—Montefiore Hospital

Twelve weeks; 1:00 to 4:00 pm, Thursdays, February 19–May 14, 1942, Fee, \$50 00

Diagnosis of the Kidneys and Arteries—Mount Sinai Hospital

Twelve weeks; 4:00 to 5:00 pm, Thursdays, December 11, 1941–February 19, 1942, Fee, \$15 00

Advanced Course in Diseases of the Heart—Mount Sinai Hospital

Ten weeks, 10 30 a m to 12 30 p m, Fridays, February 6–April 17, 1942, Fee, \$50 00

Advanced Course in Clinical Electrocardiography—Mount Sinai Hospital

Eight weeks, 8 30 to 10 30 a m, Fridays, February 6–April 3, 1942, Fee, \$35 00

Diseases of Metabolism and Practical Dietetics—Mount Sinai Hospital

Eight weeks, 2 00 to 3 30 p m, Mondays, Wednesdays and Fridays, February 2–March 27, 1942, Fee, \$40 00

Intensive Course in Cardiovascular Diseases—Mount Sinai Hospital

Four weeks, full time, April 6–May 2, 1942, Fee, \$100 00

Intensive Course in Gastro-enterology—Mount Sinai Hospital

Four weeks, full time, April 6–May 2, 1942, Fee, \$100 00

Intensive Course in Medicine—Mount Sinai Hospital

Four weeks, full time, May 4–29, 1942, Fee, \$100 00

General and Special Pathology—Mount Sinai Hospital

Nine weeks, 8 30 to 10 00 a m, Thursdays and Fridays, February 3–April 10, 1942, Fee, \$45 00

Surgical Pathology—Mount Sinai Hospital

Nine weeks, 8 30 to 10 00 a m, Tuesdays and Fridays, April 21–June 26, 1942, Fee, \$45 00

Diseases of Children—Clinical Measurements of Intelligence—Mount Sinai Hospital

Six weeks, 2 00 to 3 00 p m, Wednesdays, February 4–March 25, 1942, Fee, \$15 00

Courses for Specialists

Gastrosocopy—Presbyterian Hospital

Three afternoons weekly for two months, dates and hours by special arrangement, Fee, \$200 00

Clinical Radiotherapy—Affiliated Hospitals

Three months, full time, March 30–June 26, 1942, Fee, \$250 00

(This institution and affiliated hospitals offered numerous courses in medicine and medical specialties from October to December, 1941, but because these courses were already underway, they have been omitted)

Duke University School of Medicine

Wilburt C Davison, M D, Dean

Durham, N C

This institution conducts clinics and demonstrations in medicine and other specialties 9 00 a m to 12 30 p m every Saturday, clinical pathological conferences at 5 00 p m every Friday and medical staff rounds at 11 30 a m every Friday, which all physicians may attend. In addition, the University offers without charge postgraduate internships to practicing physicians for one or two weeks, and in cooperation with the North Carolina State Board of Health, the U S Children's Bureau and the School of Public Health of the University of North Carolina, also offers weekly postgraduate courses in obstetrics and pediatrics

Georgetown University School of Medicine
 David V. McCauley, S J, Ph D Dean
 3900 Reservoir Rd, N W
 Washington, D C

Postgraduate work at the Georgetown University School of Medicine is limited to a series of fellowships in internal medicine, pathology, pediatrics, radiology, dermatology and syphilology. The course of study in each of these fields extends over a period of at least three years. The University will confer the degree of Doctor of Medical Science upon those graduate students who satisfy the Council on Graduate Medical Studies that they possess the ability to have made adequate progress and to have made a real contribution to the field of knowledge of their respective specialties.

Harvard Medical School
 Courses for Graduates
 C Sidney Burwell, M D, Dean
 Frank R. Ober, M D, Assistant Dean
 25 Shattuck St
 Boston, Mass

This institution has announced the following program of postgraduate courses in internal medicine and the allied specialties for the 1941-42 session

203—*General Course in Internal Medicine*

A one-month course given during April, May, August and September at the Boston City Hospital; during June and October, at the Peter Bent Brigham Hospital; during November, at the Massachusetts General Hospital. Unlimited registration, Fee, \$150 00, Registration Fee, \$5 00

206—*Selected Subjects in Endocrinology and Metabolism*

Dr Fuller Albright at Massachusetts General Hospital
 August 3-15, 1942; Fee, \$80 00, Registration Fee, \$5 00

209—*Clinical Allergy*

Dr Francis M Rackemann at Massachusetts General Hospital
 July 6-17, 1942, 9 00 a m to 1 00 p m weekdays, with two afternoon sessions each week; no Saturday sessions, registration limited to men, Fee, \$50 00; Registration Fee, \$5 00

223—*Principles and Practice of Gastro-enterology*

Dr E Stanley Emery at Peter Bent Brigham Hospital
 July, 1942, five days a week, mornings and afternoons, Fee, \$100 00

226—*Diagnosis and Treatment of Heart Disease*

Dr Edward F. Bland, Dr Howard B Sprague and Dr. Paul D White at Massachusetts General Hospital and House of the Good Samaritan
 April and May, 1942, 2 30 to 4 30 p m, Fridays, Fee, \$25 00

228—*Cardiology*

Dr Paul D White, Dr Howard B Sprague, Dr Edward F Bland and Associates at Massachusetts General Hospital
 August, 1942, six mornings and four afternoons a week, Fee, \$150 00, Registration Fee, \$5 00

231—*Advanced Cardiology*

Dr Paul D White, Dr Howard B Sprague, Dr Edward F. Bland and Associates at Massachusetts General Hospital

September, 1942, six mornings and four afternoons a week, Fee, \$150 00, Registration Fee, \$5 00

230—*Internal Medicine—Diagnosis and Treatment*

Dr F Dennette Adams and Associates at Massachusetts General Hospital
June 22–July 31, 1942, daily, except Saturday afternoon, Fee, \$200 00,
Registration Fee, \$5 00

231—*Modern Diagnosis and Treatment of Heart Disease*

Dr Samuel A Levine and Dr Eugene C Eppinger and Associates at Peter
Bent Brigham Hospital
July, 1942, daily, Fee, \$150 00, Registration Fee, \$5 00

233—*Diabetes*

Dr Howard F Root and Dr Alexander Marble at New England Deaconess
Hospital Registration Fee, \$5 00

244—*Cardiology*

Dr Paul D White, Dr Burton E Hamilton, Dr Samuel A Levine, Dr
Ashton Graybiel and Associates at Massachusetts General Hospital, Boston
City Hospital, Peter Bent Brigham Hospital and Harvard Medical School
Full-time, twelve-month course, beginning July 1, 1942, admission subject to
the approval of instructor, Fee, \$600 00, Registration Fee, \$5 00

This institution also conducts three full-time, twelve-month courses in internal
medicine, beginning early in September, under Dr James H Means and Associates
at the Massachusetts General Hospital, under Dr George R Minot, Dr Laurence B
Ellis, Dr W Richard Ohler and Associates at the Boston City Hospital, and under
Dr Soma Weiss and Associates at the Peter Bent Brigham Hospital. Admittance to
these courses is limited to a small group and admission is subject to the approval of the
instructor. Fee, \$300 00, Registration Fee, \$5 00

Long Island College of Medicine

Jean A Curran, M D, Dean
350 Henry St
Brooklyn, N Y

Postgraduate courses at the Long Island College of Medicine are conducted under
the auspices of the Joint Committee on Postgraduate Education of the College and
the Medical Society of the County of Kings. The Committee offers a series of three
programs during the year. The courses include various branches of medicine and
surgery and consist of lectures, demonstrations and clinics at a number of participating
hospitals. All of the courses are part-time and are offered for two hours or more
one day each week. Any graduate of a registered medical school is eligible to attend
and the fee varies in accordance with the number of sessions. The winter program
has not yet been announced.

New York Medical College

J A W Hetrick, M D, Acting Dean
1 E 105th St
New York, N Y

This institution offers a three-year full-time course, eight months each year,
to qualified physicians in the basic and fundamental work of internal medicine, leading
to the degree of Master of Medical Science. During this period the student receives
an appointment as a non-resident fellow in medicine. The last two years of the course

are spent in an approved residency and in research work. A thesis is required for graduation.

Short courses in Electrocardiography, Peritoneoscopy and Gastrosocopy are also offered; dates and fees not announced.

New York University College of Medicine
John H. Mulholland, M.D., Assistant Dean
477 1st Ave.
New York, N. Y.

Graduate Study in Medicine

A full-time three-year course is offered to a limited number of recent graduates in medicine who have had at least two years of internship or its equivalent to pursue graduate work in internal medicine. Problems pertaining to the basic medical sciences as applied to clinical medicine are developed by the students under the guidance of a member of the faculty of the Department of Medicine and in conjunction with other departments of the College of Medicine, according to the nature of the study. Registration Fee, \$12.00 for each year of work.

The following short courses are offered:

Internal Medicine

Five mornings a week for a period of one month, 9:00 a.m. to 12:00 m., eight sessions during the year from October through May, Fee, per session, \$50.00.

Course designed for physicians in general practice desiring a practical review of recent advances in diagnosis and treatment.

Clinical Electrocardiography—Louis F. Bishop, Jr., M.D.

Fifteen weeks, 2:30 to 4:30 p.m., Mondays, February 2–May 11, 1942, Fee, \$50.00.

Interpretation of the electrocardiogram and its practical application is presented, as well as measurement and analysis of a large number of curves, operation of standard instruments, normal and abnormal electrocardiograms.

Pneumonia—Jesse C. M. Bullowa, M.D., and Staff

Four-week sessions throughout the year, six days a week, 9:00 a.m. to 5:00 p.m., Fee, \$100.00.

Course includes clinical, radiological, and bacteriological studies of acute respiratory infections, and demonstrations of the diagnosis, course, treatment, pathology, and radiographic appearances of pneumonia.

Radiology—I. Seth Hirsch, M.D., Charles Gottlieb, M.D., and Staff.

Three-month course, 4:00 to 6:00 p.m., Mondays, Wednesdays and Fridays, during the spring and fall sessions, Fee, \$100.00.

The course presents general roentgen-ray diagnosis, designed for the general practitioner in medicine and consists of lectures, practical demonstrations and conference.

Diseases of the Liver and Biliary Tract—Manfred Kraemer, M.D.

Four weeks, five sessions of two hours each, 9:00 to 11:00 a.m., Wednesday, January 7 through February 4, 1942, at Newark (N. J.) City Hospital.

The course will present a comprehensive review of diseases of the liver and biliary tract designed to familiarize the general practitioner with recent advances in diagnosis and treatment. It will consist of illustrated lectures, presentation of cases and laboratory procedure.

Tufts College Medical School
 Postgraduate Division
 Samuel Proger, M D, Chairman
 30 Bennet St
 Boston, Mass

The courses announced below are designed for the busy general practitioner who wishes to bring his knowledge up to date. The work is largely given in the New England Medical Center. In addition to the tuition fee noted below, there is a \$5.00 registration fee which covers all courses taken within a twelve-month period.

Allergy—Ethan Allan Brown, M D

Five days, May 18-22, 1942, Fee, \$25.00

Cardiology—Samuel Proger, M D

Five days, May 4-9, 1942, Fee, \$25.00

Dermatology A—Francis M. Thurmon, M D

One week, May 18-23, 1942, Fee, \$25.00

Dermatology B—William P. Boardman, M D

One week, January 19-24, 1942, Fee, \$25.00

Diabetes—Joseph Rosenthal, M D

One week, January 19-24, 1942, Fee, \$25.00

Diseases of the Bone and Joints—Heinrich G. Brugsch, M D

One week, March 2-7, 1942, Fee, \$25.00

Electrocardiography—Heinz Magendantz, M D

Five days, May 11-15, 1942, Fee, \$25.00

Advanced Electrocardiography—Heinz Magendantz, M D

Three days, January 26-28, 1942, Fee, \$20.00

Endocrinology—Charles H. Lawrence, M D

Five days, May 25-29, 1942, Fee, \$25.00

Gastro-enterology—Katherine S. Andrews, M D

One week, February 9-14, 1942, Fee, \$25.00

Hematology C—William Dameshek, M D

Two weeks, July 6-18, 1942, Fee, \$75.00

Hematology D—William Dameshek, M D

Nine weeks, 3:30 to 5:00 p m, Wednesdays, March 4-April 29, 1942, Fee, \$15.00

Internal Medicine—Samuel Proger, M D

Four weeks, May 4-29, 1942, Fee, \$50.00

Pediatrics—Elmer W. Barron, M D

Four weeks, January 5-31, 1942, Fee, \$50.00

Radiology—Alice Ettinger, M D

Four days, January 13-16, 1942, Fee, \$25.00

Fellowships

Through the Bingham Associates Fund, fellowships for postgraduate study are available for physicians practicing in Maine, who are members of the Maine Medical Association. Application should be made to the Chairman. These fellowships are

not available to other New England physicians, the tuition fees, however, are placed at a level calculated to make the courses available to the great body of physicians in New England

Tulane University of Louisiana School of Medicine
H W Kostmayer, M D, Director of Department of Graduate Medicine
1430 Tulane Ave
New Orleans, La

Review Course in Internal Medicine

Six weeks, beginning January 5 and February 18, 1942, Fee, not announced

Assistantships

This institution offers to a limited number of properly qualified physicians opportunities to become assistants in the Department of Medicine and to participate in the teaching activities of the staff. Such individuals have assigned reading and research opportunities and, in some instances, may shape their work to lead to the degree of Master of Science in Medicine after a period of not less than two years.

Throughout the year the Department of Graduate Medicine arranges on demand short intensive courses in certain subjects, such as cardiology, pediatrics, etc

University of California Medical School
Robert G Sproul, M D, Acting Dean
The Medical Center
San Francisco, Calif

The Medical School offers two short refresher courses each year, one in January and one in June. A course in "Clinical Aspects of New Therapy" will be offered January 5-7, 1942. This course will be intensive and is designed to meet the needs of practicing physicians. It will include Sulfonamide Drugs, Drugs Used on Central Nervous System, Organotherapy, Drugs Used in Treatment of Diseases of the Adrenal Glands, New Drugs Acting on the Heart and Circulation, and Clinical Aspects of Nutrition. Registration Fee, \$20.00. The subject of the June, 1942, course has not yet been announced.

University of Chicago, The School of Medicine
Victor Johnson, M D, Dean of Medical Students
58th St & Ellis Ave
Chicago, Ill

Postgraduate work leading to the degree of Master of Science, or the degree of Doctor of Philosophy, may be taken in the clinical departments of the University. Usually one year of work is required for the degree of Master of Science and three years of work for the degree of Doctor of Philosophy. Individual programs, including research work, are planned in consultation with the department in which the work is taken.

This institution also offers the following intensive courses in Gastroscopy under the direction of Dr. Rudolf Schindler:

Advanced Gastroscopy

Course given for a three-month period during the summer, autumn and winter quarters, and is limited to one student per quarter, Fee, \$150.00

Gastrosocopy

Two-week course given each month during the summer, autumn and winter quarters, and is limited to three students, Fee, \$100 00

University of Cincinnati College of Medicine

Stanley Dorst M D, Dean

Eden & Bethesda Aves

Cincinnati, Ohio

Cardiology

A two-week intensive course in cardiology is offered by the College of Medicine in cooperation with the Heart Council of the City of Cincinnati during September of each year, Fee, \$75 00

Diabetes

An intensive refresher course in weekly sessions in the treatment of diabetes is offered each spring by the College of Medicine and the Diabetic Council of the City of Cincinnati, exact dates and fees not announced

University of Georgia School of Medicine

G Lombard Kelly, M D, Dean

University Pl

Augusta, Ga

The School of Medicine offers only short courses in Electrocardiography, arrangements for which are made on request to Dr Virgil P Sydenstricker, Professor of Medicine

University of Illinois College of Medicine

David J Davis M D, Dean

1853 W Polk St

Chicago, Ill

Postgraduate work is limited to candidates for the degree of Master of Science or Doctor of Philosophy These courses are full time and require one to three years of study

University of Kansas School of Medicine

Harry R Wahl, M D, Dean

39th St & Rainbow Blvd

Kansas City, Kan

Refresher Courses

The School of Medicine offers four-day refresher courses in all fields of medicine each spring Work in the sub-specialties of internal medicine, such as heart, chest and tuberculosis, is included No registration fee for physicians residing in Kansas

University of Vermont College of Medicine

C H Beecher, M D, Chairman, Committee of Administration

Pearl St

College Park, Burlington, Vt

General Medicine

Each spring, usually during May, the College of Medicine in cooperation with the Vermont State Medical Society conducts a graduate assembly in general medicine

This assembly consists of lectures, clinics, demonstrations, round table discussions and clinical-pathological conferences, conducted by the faculty members of the College. No admission fee for Vermont physicians.

University of Wisconsin Medical School
William S. Middleton, M.D., Dean
408 N. Charter St.
Madison, Wis.

In addition to the opportunities in residencies and research fellowships, the University of Wisconsin Medical School has made the following announcement:

Observation courses have been organized by the Medical Faculty and Staff of the State of Wisconsin General Hospital upon the approval of the Regents of the University of Wisconsin. No stereotyped courses or lectures are afforded, but attendance upon lectures, clinical services and staff meetings of the Hospital is arranged. A stated fee is charged all physicians in attendance upon the clinical services for periods exceeding one (1) month. This fee shall be \$100.00 per month or \$400.00 per semester and shall be credited to the department to which the physician is assigned. A certificate of attendance shall be granted upon the completion of the course and shall be signed by the President, Dean of the Medical School and chief of the responsible department. No credit toward an advanced degree may be earned by such attendance, nor is it purposed to include the existing residencies in the scope of this recommendation.

Each spring the Medical School offers a one-week course in medicine and pediatrics, Registration Fee, \$7.50.

Vanderbilt University School of Medicine
John B. Youmans, M.D., Director of Postgraduate Instruction
21st St. at Edgehill
Nashville, Tenn.

1 *Medicine*

These courses, which are designed primarily for the holders of Commonwealth Fund fellowships, are given during the summer from approximately mid-June to mid-July. The course is of one month's duration and consists of seminars, conferences and practice work in the wards and the outpatient department in Internal Medicine and allied specialties of dermatology, neurology, psychiatry, metabolic diseases, allergy, diseases of the chest and syphilis.

It is designed to review this field for the general practitioner and acquaint him with the advances in diagnosis and treatment. A limited number of physicians in addition to the holders of Commonwealth Fund fellowships will be accepted under certain conditions. Tuition, \$50.00.

2 *Syphilis—Medicine 12*

This course is open to county health officers and physicians with appointments in public health units. It is designed to familiarize the health officer with all aspects of the syphilis problem. It offers him the opportunity of studying the individual patient, history taking, physical examination, darkfield and lumbar puncture procedures and treatment.

The student attends each clinic session for a period of four weeks and assists in the conduct of the clinic. A series of lectures early in the course is given to review the clinical and epidemiological aspects of syphilis. The remainder of the time is devoted to field work, under the direction of the epidemiologist. Several such courses

are given from September to April inclusive Each course is limited to six physicians
No tuition fee

5 Syphilis—Medicine 13 *Postgraduate Course in Syphilis*

This course is open to properly qualified physicians wishing to secure special training in syphilis It is designed to offer training fitting the student for positions of responsibility in syphilis control work

The physician is expected to take his place as one of the staff of the clinic, to examine and treat his patients, assuming responsibility for them Opportunity for thorough training is offered in the conduct of a syphilis clinic, the diagnosis of the disease, including darkfield and lumbar puncture procedures and in treatment Epidemiological field work is to be done under the direction of the epidemiologist of the syphilis clinic

Physicians will be accepted for such work for a period of six to twelve months, dependent upon the needs of the individual physician No tuition fee

1 Syphilis B. *Demonstration in Syphilis Clinic Management for Physicians and Nurses*

This course is open to physicians and registered nurses It is designed to give an opportunity to physicians and nurses to observe the management of patients and clinic procedures for a period of two weeks at intervals during the year Several such courses are given from September to April inclusive No more than three physicians and two nurses will be accepted during each period No tuition fee

5 Graduate Course in Internal Medicine

This course consists of supervised work with patients in the medical outpatient service, including the related specialties, experience in the diagnostic laboratories, assigned reading, seminars and conferences, including pathological and radiological conferences and autopsy study, directed study and seminars in the pre-clinical sciences, particularly physiology and biochemistry Special investigation of a particular problem in one of the divisions of internal medicine as the basis of a thesis is required The course extends over a period of one year and is open to physicians who have completed an internship, have had an additional year's experience as assistant resident in medicine or its equivalent and are acceptable to the school Courses begin July 1 and are limited to six students Tuition fee, \$300 00

Fellowships

Three fellowships are available for this course described above These fellowships, which provide tuition, board and lodging, are open to those who meet the requirements mentioned above and will be awarded on the basis of the individual's training and recommendations

6 *Special work in the Department of Medicine may be made available by special arrangement Tuition and fees according to arrangement*

Further information regarding these courses should be addressed to the Registrar of the School of Medicine, Vanderbilt University, Nashville, Tenn

Wayne University College of Medicine

Edgar H Norris, M D, Dean

1516 St Antoine St

Detroit, Mich

This institution offers graduate courses requiring full-time study and training in a university fellowship, or in an approved medical residency in hospitals affiliated with the College of Medicine The work in these courses is designed to meet the requirements of the American Board of Internal Medicine It also offers post-grad-

uate work in the field of internal medicine on a part-time basis in cooperation with the Continuation School of the Wayne County Medical Society. The following are the continuation courses under the direct auspices of Wayne University College of Medicine

- 2 *Clinical Examination of the Heart*—William J. Seymour Hospital, Eloise
Six weeks, 2 00 to 5 00 p m, Wednesdays, February 18–March 25, 1942, Fee, \$5 00
- 3 *Clinical Electrocardiography*—William J. Seymour Hospital, Eloise
Six weeks, 2 00 to 5 00 p m, Wednesdays, January 7–February 11, 1942, Fee, \$5 00
- 28 *Review of Current Literature*—City of Detroit Receiving Hospital
1 00 to 2 00 p m, Wednesdays, specific dates not announced, no fee
- 29 *Therapeutics*—City of Detroit Receiving Hospital
Four months, 1 00 to 3 00 p m, Thursdays, January 29–May 28, 1942, Fee, \$10 00

Woman's Medical College of Pennsylvania
Margaret D. Craighill, M D, Dean
Henry Ave. & Abbottsford Rd.
East Falls, Philadelphia, Pa

Clinical Cardiology—William G. Leaman, Jr, M D, Director

An intensive course covering the clinical application of present day knowledge of heart disease will be presented in two four-hour periods a week, for a period of twelve weeks, beginning January 2, 1942. Case presentations in the ward and the outpatient department are supplemented by exercises in the interpretation of the electrocardiogram and roentgen methods of cardiac diagnosis. The course is given in sections of not less than four, nor more than ten students. Men and women are admitted for this special work, Fee, \$100 00

Part III—Postgraduate and Clinical Meetings

The American College of Physicians
4200 Pine St
Philadelphia, Pa

In the November, 1941, issue of this journal the College program of one- and two-week intensive postgraduate courses was announced in detail. The following courses, arranged through the generous cooperation of the directors and the institutions at which courses will be given, have been arranged

February, 1942, Courses

- 1 *Allergy*—The Roosevelt Hospital, Department of Allergy, New York, N Y
Robert A. Cooke, M D, F A C P, Director
2 weeks, February 2–14, Fee, \$40 00
- 2 *The Diagnosis and Treatment of Heart Disease*—Massachusetts General Hospital and the House of the Good Samaritan, Boston, Mass
Paul D. White, M D, F A C P, Director
2 weeks, February 2–14, Fee, \$40 00
- 3 *General Medicine*—University of California Medical School and Stanford University School of Medicine, San Francisco, Calif

William I Keir, M D , F A C P , and Arthur L Bloomfield, M D , F A C P , Directors

2 weeks, February 2-14, Fee, \$40 00

- 4 *Internal Medicine*—Johns Hopkins University School of Medicine and University of Maryland School of Medicine, Baltimore, Md

Warfield T Longcope, M D , F A C P , and Maurice C Pincoffs, M D , F A C P , Directors

2 weeks, February 2-14, Fee, \$40 00

- 5 *Gastrointestinal Diseases*—Graduate Hospital, University of Pennsylvania, Philadelphia, Pa

Henry L Bockus, M D F A C P , Director

1 week, February 2-7, Fee, \$20 00

Pic-Meeting Courses

- 6 *Allergy*—Washington University School of Medicine and Barnes Hospital, St Louis, Mo

Harry L Alexander, M D , F A C P , Director

2 weeks, April 6-18, Fee, \$40 00

- 7 *Arthritis and Rheumatic Diseases*—The Mayo Foundation, University of Minnesota, and The Mayo Clinic, Rochester, Minn

Philip S Hench, M D , F A C P , Director

1 week, April 13-18, Fee, \$20 00

- 8 *Peripheral Vascular Diseases, Including Hypertension*—The Mayo Foundation, University of Minnesota, and The Mayo Clinic, Rochester, Minn

Edgar V Allen, M D , F A C P , Director

2 weeks, April 6-18, Fee, \$40 00

- 9 *Gastrointestinal Diseases*—University of Chicago, The School of Medicine, Billings Hospital, Chicago, Ill

Walter L Palmer, M D , F A C P , Director

2 weeks, April 6-18, Fee, \$40 00

- 10 *Internal Medicine*—University of Minnesota Medical School, Minneapolis, Minn

Cecil J Watson, M D , F A C P , Director

2 weeks, April 6-18, Fee, \$40 00

- 11 *Tuberculosis*—University of Colorado School of Medicine and Hospitals, Denver, Colo

James J Waring, M D , F A C P , Director

1 week, April 13-18, Fee, \$20 00

The Twenty-sixth Annual Session of the College, covering internal medicine and its allied specialties and consisting of General Sessions, Special Lectures, Panel Discussions, Hospital Clinics and Demonstrations, will be held in St Paul, Minn, April 20-24, 1942, with headquarters at the Hotel Lowry and Hotel St Paul

For Bulletin of Postgraduate Courses and Program of the Annual Session, send requests to the College

Colorado State Medical Society
537 Republic Bldg
Denver, Colo

The 10th Annual Midwinter Postgraduate Clinics will be held in Denver Colo, February 19-21, 1942 The meeting will consist of morning lectures, utilizing the

facilities of several of the local hospitals, and afternoon lecture sessions Program and registration fee, not announced.

For the three days immediately preceding the Postgraduate Clinics the Colorado State Medical Society and the University of Colorado School of Medicine will conduct intensive refresher courses Subjects and fees, not announced

Dallas Southern Clinical Society
1133 Medical Arts Bldg
Dallas, Tex

The Society has launched a program of courses for the Continuation of Medical Study to be held each year during June, October and January Intensive courses for the general practitioner and specialist are held in the various branches of medicine and surgery for three-day periods The courses will be conducted at the hospitals and clinics of Dallas and at Baylor University College of Medicine, and will consist of round table discussions, clinics, demonstrations and pathological conferences Courses are open to all physicians who are members of a county medical society, registration fee, \$5 00

In addition to the Continuation Courses the Dallas Southern Clinical Society holds an annual Spring Clinical Conference during March of each year This meeting consists of general assemblies, postgraduate teaching, clinics, round tables, clinical-pathological conferences and scientific and technical exhibits Any physician who is a member of a county medical society may register Registration fee, \$10 00

New York Academy of Medicine
2 E 103rd St
New York, N Y

During October of each year this society conducts a Graduate Fortnight consisting of morning panel discussions, afternoon hospital clinics, evening addresses, scientific exhibits and demonstrations The subject of the 1942 Graduate Fortnight has not yet been announced Registration limited to the medical profession, Fellows of the Academy admitted without fee, all others, \$5 00

During the fall and winter each year, the New York Academy of Medicine sponsors a series of Friday afternoon lectures at 4 30 p m These lectures are open to the medical profession and to medical students The following is the program of lectures for this winter

- December 5, 1941, *Cirrhosis of the Liver*—Arthur J Patek, Jr, M D ,
- December 12, 1941, *Certain Aspects of the Selectivity and Side Reactions of the Sulfonamide Drugs*—William S Tillett, M D ,
- December 19, 1941, *Recent Advances in Knowledge of Bright's Disease*—Arthur M Fishberg, M D ,
- January 9, 1942, *Evaluation of Methods of Treating Cancer of the Female Breast*—Frank E Adair, M D ,
- January 16, 1942, *Clinical Chemistry in General Practice*—William T Salter, M D ,
- January 23, 1942, *Plasma Proteins in Health and Disease*—Robert F Loeb, M D ,
- January 30, 1942, *Interrelationships of Ophthalmology and Systemic Diseases*—R Townley Paton, M D ,
- February 6, 1942, *Prophylactic Treatment of Rheumatic Fever by Sulfanilamide*—Caroline Bedell Thomas, M D ,
- February 13, 1942, *The Pathogenesis, Recognition and Treatment of Gout*—John H Talbott, M D ,

- February 27, 1942, *Modern Methods of Diagnosis in Disorders of the Gallbladder*—R Franklin Carter, M D ,
 March 6, 1942, *Indications for Surgery and the Surgical Treatment of Diseases of the Gallbladder*—Thomas H Russell, M D ,
 March 13, 1942, *Recent Advances in Certain Renal Surgical Problems*—George F Cahill, M D ,
 March 20, 1942, *Psychopathological Disorders in Childhood*—William S Langford, M D ,
 March 27, 1942, *Cancer of the Cervix and Fundus Uteri*, Panel Discussion—George Gray Waid, M D , Chairman,
 April 10, 1942, *Edema Its Pathogenesis and Treatment*—William Goldring, M D ;
 April 17, 1942, *Neuropsychiatric Aspects of Alcoholism*—Herman Wortis, M D ,
 April 24, 1942, *Rehabilitation Surgery*—Henry H Kessler, M D
-

Philadelphia County Medical Society
 21st & Spruce Sts
 Philadelphia, Pa

The 7th Annual Postgraduate Institute of the Philadelphia County Medical Society will be held in Philadelphia, April 13-17, 1942, under the direction of Dr Rufus S Reeves. The subject of this Institute will be "Modern Therapy" and will cover Arthritis, Blood Dyscrasias, Chemotherapy, Diabetes, Industrial Medicine, Nutrition, Ophthalmology, Tuberculosis and Proctology. Members of the Society are admitted without fee, others, \$5.00.

Tennessee State Medical Association
 706 Church St
 Nashville, Tenn

During 1941-42 the Tennessee State Medical Association will sponsor a series of postgraduate courses in the various branches of medicine and surgery. An outstanding instructor is selected to present in various centers throughout the state one lecture per week for a period of ten weeks. Teaching centers are established where a sufficient number of physicians are interested and the hours, day and dates arranged to suit the group in each district.

Dr Robert P McCombs will be the instructor of the postgraduate course in internal medicine. The subjects of his lectures will be *Disorders of the Heart, Cardiovascular-Renal Disease, The Management of Heart Failure and Renal Failure, Nutritional Diseases, The Anemias and Blood Dyscrasias, Diabetes Mellitus, Chronic Non-Tuberculous Pulmonary Diseases, The Uses and Abuses of Sulfanilamide, Sulfapyridine and Sulfathiazole in the Practice of Medicine, Gastrointestinal Diseases, and Chronic Arthritis*.

Wayne County Medical Society
 4421 Woodward Ave
 Detroit, Mich

The Continuation School of Wayne County, sponsored by the Wayne County Medical Society in cooperation with Wayne University College of Medicine, the hospitals of Wayne County and the Detroit Department of Health, offers a series of part-time postgraduate courses throughout the year in the various medical and surgical specialties. During 1941-42 the following courses will be offered:

ALLERGY

- 9 *Bedside Teaching in Diagnosis and Treatment of Allergic Conditions*—William J Seymour Hospital, Eloise
10 00 a m to 12 00 m, Tuesdays, weekly throughout the year, Fee, \$5 00
- 23 *Clinical Allergy*—Mt Carmel Mercy Hospital, Detroit
11 00 a m to 12 00 m, Tuesdays, specific dates not announced, Fee, \$5 00

DERMATOLOGY

- 16 *Dermatology*—The Grace Hospital, Detroit
11 00 a m to 12 00 m, Saturdays, specific dates not announced, Fee, \$5 00

DIABETES

- 6 *Bedside Teaching in General Medicine, with Particular Reference to Diabetes*—William J Seymour Hospital, Eloise
10 00 a m to 12 00 m, Saturdays, weekly throughout the year, Fee, \$5 00
- 11 *Management of Diabetes*—The Grace Hospital, Detroit
11 00 a m to 12 00 m, Wednesdays, specific dates not announced, Fee, \$5 00

GASTRO-ENTEROLOGY

- 13 *Gastro-enterology*—The Grace Hospital, Detroit
11 00 a m to 12 00 m, Thursdays, specific dates not announced, Fee, \$5 00

GENERAL MEDICINE

- 5 *Bedside Teaching in General Medicine*—William J Seymour Hospital, Eloise
11 00 a m to 12 00 m, Mondays, weekly throughout the year, Fee, \$5 00
- 7 *Bedside Teaching in General Medicine*—William J Seymour Hospital, Eloise
11 00 a m to 12 00 m, Wednesdays, weekly throughout the year, Fee, \$5 00
- 10 *General Medicine and Clinical Diagnosis*—The Grace Hospital, Detroit
11 00 a m to 12 00 m, Tuesdays, specific dates not announced, Fee, \$5 00
- 12 *Non-Tuberculous Diseases of the Chest*—The Grace Hospital, Detroit
11 00 a m to 12 00 m, Thursdays, specific dates not announced, Fee, \$5 00.
- 18 *Bedside Teaching in General Medicine*—Harper Hospital, Detroit
Two months, 11 00 a m to 12 00 m, Mondays and Thursdays, during March and April, 1942, Fee, \$5 00
- 22 *General Medicine*—Highland Park General Hospital, Highland Park
9 00 to 10 00 a m, Fridays, specific dates not announced, Fee, \$5 00

NEUROLOGY

- 8 *Bedside Teaching in Neurology*—William J Seymour Hospital, Eloise
11 00 a m to 12 00 m, Wednesdays, weekly throughout the year, Fee, \$5 00
- 19 *Neurology and Neuropsychiatry*—Harper Hospital, Detroit
Eight weeks, 11 00 a m to 12 00 m, Tuesdays, during December, 1941, and January, 1942, Fee, \$5 00

PEDIATRICS

- 21 *Pediatrics*—Henry Ford Hospital, Detroit
9 15 to 10 30 a m, Tuesdays, specific dates not announced, Fee, \$5 00

PHYSIOTHERAPY

- 14 *Physiotherapy*—The Grace Hospital, Detroit
10 00 a m to 12 00 m, Wednesdays, specific dates not announced, Fee, \$5 00

SYPHILOLOGY

- 15 *Syphilology*—The Grace Hospital, Detroit
11 00 a m to 12 00 m, Thursdays, specific dates not announced, Fee, \$5 00
- 26 *Syphilology*—Receiving Hospital, Detroit
10 00 to 11 00 a m, Fridays, specific dates not announced, Fee, \$5 00
-

School of Tropical Medicine
University of Puerto Rico
San Juan Puerto Rico

Starting November 5, 1941 and ending January 21, 1942, a series of lectures on Tropical Medicine will be presented at the School of Tropical Medicine, San Juan, Puerto Rico, by various members of the department of Medicine. The following subjects are to be discussed: Lymphogranuloma inguinale, sprue, pellagra, ariboflavinosis and other deficiency diseases, Weil's disease, yaws, rat-bite fever, typhoid fever, paratyphoid A and B, amebic dysentery, tropical lymphangitis, clinical aspects of intestinal parasites, malarial fevers and blackwater fever, and schistosomiasis mansoni.

The lectures will be given by Dr Ramon M Suárez, F A C P, head of the Department of Medicine of the School, by Dr R Rodríguez-Molina, F A C P, and by Dr F Hernandez Morales.

MINUTES OF THE BOARD OF GOVERNORS

BOSTON, MASS

April 21, 1941

The first meeting of the Board of Governors, in conjunction with the Twenty-fifth Annual Session of the American College of Physicians, convened in the Hancock Room, Hotel Statler, Boston, Mass., Monday, April 21, 1941, at 5 15 p.m., with Dr Charles H Cocke, Chairman, presiding, and the following in attendance

Dr James F Churchill, Dr James J Waring, Dr Charles H Turkington, Dr Wallace M Yater, Dr Cecil M Jack (representing Dr Samuel E Munson), Dr Robert M Moore, Dr Thomas Tallman Holt, Dr William B Breed, Dr Warren Thompson, Dr Nelson G Russell, Dr Leander A Riely, Dr Edward L Bortz, Dr John L Calene, Dr J Owsley Manier, Dr Tomas Guardia Guardia (representing Dr William M James), Dr J. Howard Holbrook, Dr Oliver C Melson, Dr Ernest H Falconer, Dr Benjamin F Wolverton (representing Dr Fred M Smith), Dr W S Kerlin (representing Dr Joseph E Knighton), Dr Henry R Carstens, Dr Edga. V Allen, Dr A Comingo Griffith, Dr George H Lathrope, Dr Charles H Cocke, Dr Julius O Arnson, Dr Alexander M Burgess, Dr Paul K French, Dr Walter B Martin, Dr Charles E Watts, Dr Hugh A Farris, Dr Charles F Moffatt, Dr Fred W Wilkerson, Dr Lewis B Flinn, Dr Turner Z Cason, Dr Ernest B Bradley (representing Dr C W Dowden), Dr Eugene H Drake, Dr Louis Krause, Dr John G Archer, Dr Charles F Tenney, Dr A B Bower, Dr Homer P Rush, Dr M. D Levy, Dr Karl H Doege (representing Dr Elmer L Sevringhaus), Dr George F Strong and Dr John M McCants (representing Dr Ross T McIntire)

The Secretary, Mr E R Loveland, read abstracted Minutes of the preceding meetings held at Cleveland, 1940, which were approved as read

Chairman Cocke introduced President James D Bruce, who addressed the Board primarily on the subject of continuing education and the work of the American College of Physicians in connection with its postgraduate program

The Executive Secretary made a full report to the Board on the College membership during the preceding year, including deaths, life membership, elections to Associateship and Fellowship, and similar matters. He also distributed a copy of the 1941 Balance Sheet and other financial data for the information of the Board. Each Governor was given a mimeographed list of the candidates recommended for election at the current meeting by the Committee on Credentials

Chairman Cocke announced to the Board the election to Mastership of former President James Alex Miller. He also announced the election to Fellowship in the College of a group of prominent Cuban physicians, and announced that until further regulations are adopted, Cuba would be included in the territory for which the Governor of Florida is responsible

Dr Turner Z Cason, Governor for Florida, stated that he had been interested for several years in bringing into the College a number of men from Cuba, particularly from the University of Havana, and that after the group had been carefully organized and investigated, they had been invited to attend the Florida Regional Meeting of 1940, when the Florida contingent had met them all personally and discussed their type of practice. At this Regional Meeting the Chairman of the Board of Governors, Dr Cocke, and the Executive Secretary of the College, Mr Loveland, were guests and presented addresses concerning the College activities, aims and standards. Dr Cason assured the Board that the new Cuban members were men of the highest type who will do honor to the College, and that other candidates from

Cuba will be carefully examined and investigated, and the high standards maintained. He felt that nothing that has been done recently should encourage better relations between Cuba and the United States than the election of these outstanding Cuban physicians. Many of these men have in the past gone to Europe for graduate study, and their election and association with the College will undoubtedly have a force in the future to divert more Cuban physicians to this country for their graduate training. Dr. Cason further stated that these new members will attend the College meetings and take an active part.

Chairman Cocke reported the following transactions of the Board of Regents of December 15, 1940: Adoption of the following resolution:

"Resolved, that the Board of Regents shall compliment the Board of Governors for what has already been accomplished and urge the further expansion of the program of regional meetings, that the Executive Office shall be authorized to meet incidental expenses in connection with such meetings and also to give an allowance for traveling expenses of Officers of the College who are asked to attend these meetings."

In support of this resolution, the Regents had made an appropriation of \$500.00 for 1941.

Continuing, Chairman Cocke said: "As Dr. Bruce has told you, the whole emphasis of this meeting is postgraduate education, the advantages of the College, and what it has to offer are still unknown to a great many men who are members of this College. Cultivation of the Regional Meetings is one of the best ways in which the men can be accorded the contact with the activities of the College, learn something of the advantages the College offers."

"I hope as you develop these things that these Regional Meetings will grow, because that is one of the primary functions of the College. You can do no better service to your men than by the organization of these meetings to encourage them to come to the courses and the College meetings generally."

At this point, Chairman Cocke called upon Dr. Edward L. Bortz, Chairman of the Advisory Committee on Postgraduate Courses, for a report.

DR. BORTZ: "Mr. Chairman, President Bruce and Governors. When President Bruce appointed this Committee a year ago, as you know, the Committee was made up of the Dean of Harvard Medical School, Sidney Burwell, Fred Smith of Iowa, Ernest Falconer of California, James J. Waring of Colorado, and myself as Chairman."

"We were fortunate in having the leadership of Dr. Bruce in this important matter. Dr. Bruce, as you know, has been a leader in postgraduate and graduate medical education for a great many years in this country, and it was due to his inspiring understanding and energy that the State of Michigan has taken the lead in graduate medical education in this country. It was a fortunate thing when the College honored itself in appointing him to be its President, and our Committee came along just at the time that he assumed the Presidential office."

"At this time, I want to pay tribute to the energy and enthusiasm of the members of the Committee who have worked so hard in furthering the work."

"Now, in order to find out exactly what the extent of interest was in the field of graduate medical education on the part of the members, it was necessary to send out a questionnaire and have a great many conferences and a lot of correspondence with the officials of the College and the various members to find out just what they would like to have in the way of postgraduate courses for the current year."

"Of the 4,000 questionnaires sent out, we had a return of almost 1,000, which, in our opinion, is a very excellent return."

"Of the 918 or 920 questionnaires that were returned, more than half of those men signified the desire to take a course of some sort in one of these postgraduate courses, such as cardiology, gastro-enterology, hematology, allergy or neurology."

"The Committee organized ten courses, and made a recommendation to the Board of Regents that these courses be given

"This Committee is a fact-finding Committee and is not an executive committee; it has no power of its own to carry on any courses, it studies the situation and makes proper recommendations to the Executive Committee of the College and to the Board of Regents, and that is the body under the President which finally acts and okays and activates the whole movement, as it were

"In passing, I want to say to you that this work could not have been consummated and the whole program would not have been possible had it not been for the unfailing cooperation and wise, helpful guidance that the Committee has received from Mr Loveland, who worked day and night with the Committee, and when we got off the wise course many times, he got us back on the right course, so that I feel very grateful to Mr Loveland for the help he gave us

"Now, we found out that a good many of the men wanted to take courses, not only just before the Annual Session, but they wanted to have courses at other times of the year Therefore, a recommendation was made that the Board of Regents, the Executive Committee, establish some courses to be given in February We were so late in getting out the information and the publicity on it, but, even so, the courses that were given, with the exception of one course in Allergy, were outstandingly successful

"It was my good privilege to have attended the course at the Mayo Clinic, the first course ever given at the Mayo Clinic under the auspices of the College Dr Allen organized a course there and this was attended by thirty-five men I had the opportunity of talking to practically all of them, and then Dr Cocke talked with the Director of the Mayo Foundation He told us 'I am free to say to you that in all the experience of the Mayo Clinic, we have never had a group of men so enthusiastic, so well trained, so ready for advanced instruction in medicine as this group that has been sent to us by the American College of Physicians From now on, we want to cooperate with you in every way we possibly can'

"The men who attended that course and the other courses were very enthusiastic about the instruction that they received These men aren't going to these courses for the purpose of getting what the men used to go to Vienna for, a diploma to put up on the wall and prove that they were specialists, they don't care about that They are interested in qualifying themselves to be better internists

"We think this movement is the finest thing of its kind that the American College of Physicians has undertaken, and it is one of the great responsibilities that the College has to carry on, now, and in the future

"The Committee believes that certain courses should be given next year, as follows

Two Courses in General Medicine—of two weeks' duration,

Two Courses in Cardiovascular Disease—of two weeks' duration,

Two Courses in Gastrointestinal Disease—one of two weeks' duration and one of one week's duration,

One Course in Hematology, or Arthritis and Rheumatism—of one week's duration,

One Course in Tuberculosis—of one week's duration

"We believe these courses should be organized as soon as possible, after the Board of Regents has decided where the Annual Session is going to meet next year, and then if the Board of Regents authorizes the Committee to go ahead, and provided it is the same Committee, this Committee is only appointed from year to year, it will make proper contacts and have the courses arranged so that the adequate publicity can be given to these courses early in the summer

"With that in mind, men will have sufficient time to decide what courses they want to attend, and also the men who give the courses will have an adequate opportunity to organize the personnel of the institutions which are selected

"I want to thank the Board of Governors who were so gracious in sending comments and criticisms. It has been an inspiration to me and every one on the Committee to participate in this great and significant movement in medical education in the United States"

Chairman Cocke then called upon Dr. Edgar V. Allen, of Rochester, Minn., for a report

DR. ALLEN: "Chairman Cocke, President Bruce and Governors: This is our first experience in Rochester in having a course in postgraduate medical education. I can say very honestly that I am sure those who participated in the course enjoyed it more than those who were subjected to the course. The men who came, thirty-five in number, were subjected to eight hours a day for two weeks, and that is quite a bit. They are always alert, interested, ask many questions and in many instances ask questions which go to the very advanced information about the field in which we were giving the courses of advanced instruction.

"I can speak for our organization in saying that it was a pleasure for us to have this group and that we hope in the future we shall be called upon again, and if, by any chance, we are, we shall try to do it at least as well as we did in February, and, of course, we shall try to do it better."

Chairman Cocke then asked for questions from the Governors on the subject. Dr. Robert M. Moore, Governor for Indiana, described the intensive postgraduate course organized and given by the Indiana State Medical Association, and inquired if this course might also be listed as available for the College group. He said there is a definite course in Internal Medicine, and suggested the possibility that since the University Hospital and the University have all the machinery and adequate material available some course for the College might be given there. Chairman Cocke stated that the suggestion would be taken under consideration by the College Committee.

At this point, Chairman Cocke read a number of items from the Minutes of the Board of Regents of December 15, 1940, for the enlightenment of the Board of Governors, concerning regulations for the admission of non-members to postgraduate courses, the limitation of the volume of the 'Annals' to 2,400 pages per annum, the membership of the American College of Physicians on the National Research Council and the appropriation by the College of funds for the support of research in the National Research Council, including an appropriation for classification of internists in the office of Dr. James E. Paullin. Chairman Cocke also read a resolution of the Board of Regents regarding the appointment of a Committee to investigate the feasibility of establishing courses of instruction in Internal Medicine for the personnel of General Hospitals to be established by the Army, also a resolution providing \$1,800.00 to cover reprinting of the College History for an adequate supply for future Fellows and Associates of the College.

At this point, Chairman Cocke asked for reports of Regional Meetings that had been held by various Governors.

Dr. Ernest H. Falconer, Governor for Northern California, reported a College Regional Meeting at San Francisco at the time of the Pacific Coast Interurban Society's meeting. Having the meeting at the same time as the Interurban Society was planned so that there would be increased attendance, for many College members belong to both organizations. About forty members were in attendance, as were also Governor Watts of Washington and Dr. S. Marx White of Minneapolis and Governor Strong of Vancouver. Dr. Falconer stated that many members of the College had very little conception of what this organization is doing in the way of postgraduate education. Some thought that the College was trying to educate the general practitioner. The

meeting stimulated a desire to attend more of the College Sessions and some of the Postgraduate Courses. Following the meeting, several members sent in suggestions for the coming years. Dr. Falconer expressed the opinion that the meeting had done a great deal of good and that a larger number of members would participate in the future.

Dr. R. R. Snowden, Governor for Western Pennsylvania, reported on a Regional Meeting held in Pittsburgh, and expressed both surprise and gratification with the ease with which the members were influenced to attend. As it was, about 90 per cent of the members in Western Pennsylvania were present. The meeting was addressed by Dr. George Morris Piersol, Secretary-General of the College, Dr. Edward L. Bortz, Governor for Eastern Pennsylvania, and Chairman of the Advisory Committee on Postgraduate Courses, and by Mr. E. R. Loveland, Executive Secretary of the College. Dr. Piersol's address had dealt with the standards and requirements for admission, and proved exceedingly valuable in educating the members to a better understanding of what the College means and in particular of its high standards of admission. Dr. Snowden especially recommended the feasibility of holding regional meetings in every Governor's district.

Dr. Ernest B. Bradley, former President and also former Governor for Kentucky, at this time serving as Alternate for Dr. C. W. Dowden, who was absent because of illness, made a brief address.

Dr. Charles F. Tenney, Governor for Eastern New York, reported upon a Regional Meeting held in New York City just two weeks previous, at which there was a program of clinics and panels in the morning, exhibits in the afternoon and lectures in the evening. This meeting actually was the Postgraduate Fortnight of the New York Academy of Medicine, but Governor Tenney had made it a practice to bring the meeting to the attention of members of the College in Eastern New York.

Again Dr. Robert M. Moore, Governor for Indiana, brought up the matter of the possibility of combining a portion of the postgraduate program of the Indiana State Medical Association at Indianapolis with a continuation of postgraduate work for members of the College, while the organization machinery is all set up.

President Bruce questioned the propriety of an attempted integration on one level, that is, of postgraduate education for the practitioner and postgraduate education for men in the specialties. Dr. Bruce referred to the North Carolina meeting of the College which he had attended. He referred to the presentations as being of the highest calibre, saying the speakers might well have been gracing positions in the best of medical schools in this country, and a few of them were, but the majority were men out of actual practice. Dr. Bruce had been impressed with the opportunity there is for members of the College to assume leadership in medical education in their communities, not only in postgraduate work of the College itself, but in the continuing education of the practitioner.

At the request of Governor Tenney, Dr. Edward L. Bortz reported on the Regional Meeting in Eastern Pennsylvania, held at Philadelphia in February. Dr. Bortz expressed the opinion that every member of the College has an obligation and a responsibility because of his membership, that he ought to contribute something to the College, even if it is nothing other than his presence at one of the meetings. Out of a total membership of approximately 250 in Eastern Pennsylvania, more than 200 had attended the Regional Meeting. Obviously the number of members is too large for the Governor to personally contact them, and, therefore, Dr. Bortz had appointed a so-called Governors' Committee of about fifteen members, asking each of them to contact a certain group of members and seeing that they would be in attendance. A luncheon was held at the College Headquarters, followed by an afternoon scientific session at Jefferson Medical College and the evening by a cocktail hour and dinner at the Penn Athletic Club, with some special addresses.

These Eastern Pennsylvania Regional Meetings, said Dr Bortz, are looked upon by the members as the most enjoyable medical meetings of their type anywhere, and the members are looking forward already to the one in the coming year. These meetings are extending the influence and the interest in the College in Eastern Pennsylvania, they are telling younger men about the work of the College, they are becoming interested to become members. The American College of Physicians has a beneficial influence on the whole group of doctors throughout Eastern Pennsylvania. At the Eastern Pennsylvania meeting, Dr Bortz had invited the Governors of the surrounding States. Governor Tenney, of Eastern New York, and Governor Flinn, of Delaware, and Governor Burgess, of Rhode Island, were in attendance.

Governor Flinn, of Delaware, spoke further about the Eastern Pennsylvania meeting, not only had he been invited to attend, but also all of the College members in the State of Delaware. Ninety-five per cent were in attendance, and the enthusiasm locally in Delaware resulting therefrom had been greatly increased.

Dr Nelson G Russell, Governor for Western New York, stated that in lieu of a regular Regional Meeting of that district, College members had been invited to the clinical meeting of the Alumni of the University of Buffalo. Eighty members accepted the invitation, thirty-five of whom remained for the dinner in the evening. An exceptionally good program was provided.

Dr Edgar V Allen, Governor for Minnesota, stated that he wished to make it a matter of record that two of the best presentations given in connection with the College Postgraduate Course at the Mayo Clinic were those of Dr Cocke, Chairman of the Board of Governors, and of Dr Bortz, Chairman of the Advisory Committee on Postgraduate Education.

After announcements by the Chairman, the meeting adjourned at 6 20 p m.

Attest _____

Executive Secretary

MINUTES OF THE BOARD OF GOVERNORS

BOSTON, MASS

April 23, 1941

The second meeting of the Board of Governors, in conjunction with the Twenty-fifth Annual Session of the American College of Physicians, convened in the Hancock Room, Hotel Statler, Boston, Mass, Wednesday, April 23, 1941, at 12 30 p m, with Dr Charles H Cocke, Chairman, presiding, and the following in attendance:

Dr James F Churchill, Dr James J Waring, Dr Charles H Turkington, Dr Wallace M Yater, Dr Samuel E Munson, Dr Robert M Moore, Dr William B Breed, Dr Warren Thompson, Dr Nelson G Russell, Dr Leander A Riely, Dr Edward L Bortz, Dr R R Snowden, Dr John L Calene, Dr J Owsley Manier, Dr Louis E Viko, Dr J Howard Holbrook, Dr Oliver C Melson, Dr Ernest H Falconer, Dr Benjamin Wolverton (representing Dr Fred M Smith), Dr W S Kerlin (representing Dr Joseph E Knighton), Dr Henry R Carstens, Dr Edgar V Allen, Dr A Comingo Griffith, Dr George H Lathrope, Dr Charles H Cocke, Dr Julius O Arnson, Dr Alexander M Burgess, Dr Robert Wilson (representing Dr Kenneth M Lynch), Dr Paul K French, Dr Walter B Martin, Dr Charles E Watts, Dr Walter E Vest (representing Dr Albert H Hoge), Dr Hugh A Farris, Dr Charles F Moffatt, Dr Fred W Wilkerson, Dr Turner Z Cason, Dr LeRoy H Sloan, Dr Ernest B Bradley (representing Dr C W Dowden), Dr Eugene H Drake, Dr Louis Krause, Dr John G Archer, Dr Charles F Tenney, Dr A B Brower, Dr Homer P Rush, Dr M D Levy, Dr Karl H Doege (representing Dr

Elmer L. Sevringhaus), Dr George F Strong, Dr. John M McCants (representing Dr Ross T McIntire) and Dr Thomas Parran

Secretary Loveland read a resume of the minutes of the preceding meeting of April 21, which were approved as read

Chairman Cocke proceeded to new business, first being the election of a Chairman and Vice Chairman He read the By-Laws, Article VI, Section 3, governing the election of the Chairman and Vice Chairman of the Board of Governors

On motion by Dr A Comingo Griffith, seconded by Dr. Oliver C Melson, Dr Charles H Cocke was renominated as Chairman of the Board of Governors for a term of three years Nominations by resolution were closed, and the Secretary was instructed to cast the ballot for the election of Dr Cocke

On motion by Dr Alexander M Burgess, seconded by Dr Charles E Watts, Dr C W Dowden was renominated as Vice Chairman for a term of three years On motion regularly adopted, nominations were closed and the Secretary instructed to cast a ballot for the election of Dr Dowden as Vice Chairman

Accordingly, the Secretary declared the ballot cast and both Dr Cocke and Dr. Dowden reelected to the Chairmanship and Vice Chairmanship, respectively

Chairman Cocke reported the proceedings of the Board of Regents, referring especially to resolutions that had been adopted The Board of Regents commended the activity of the Advisory Committee on Postgraduate Courses and directed that there should be a continuity of effort of the Committee, with the suggestion that the present Committee be reappointed, not necessarily as it is now constituted, but with adequate continuity so that the work could go on without interruption

Thereupon Dr Cocke announced the personnel of the Committee for 1941-42 to be composed of

Edward L Bortz, *Chairman*
Ernest H Falconer
Fred M Smith
James J Waring
C Sidney Burwell

all being reappointed

Dr Nelson G Russell interrupted the proceedings to refer to the complimentary concert of the Boston Symphony Orchestra, saying it was the most inspiring affair that he had had the pleasure to attend in all of his years of going to medical meetings, and expressed the opinion that the Board of Governors should express its appreciation to the Conductor of the Orchestra and to the Committee and Dr Roger I Lee, who was responsible for the original arrangements He asked that a note of appreciation be recorded and forwarded to the Orchestra through the proper channels

The audience arose and there was long applause accorded to Dr Lee, who graciously acknowledged the ovation

At this point Dr Lee addressed the Board

Dr Lee explained how the Trustees of the Boston Symphony Orchestra and the Conductor, Dr Koussevitzky, had gladly agreed to give the Concert for the College, and if the members of the College had liked the Concert all of those locally responsible were very happy Continuing he said

"I have nothing to say as the President-Elect The President-Elect is like the fifth wheel on a spare tire on the automobile Usually, when you want it, you find that it suffers the same reverses as the other four Sometimes it isn't even inflated Whatever inflation that I may personally enjoy is the inflation of my constitution, and I hope that the inflation of the job which I am going to undertake will not be any more obvious than it is now (Laughter)

"I have always been very much interested in the work of the Board of Governors. I sat on the Board of Governors for a few years, and it has seemed to me that it has been on the whole a very wise policy of the College of Physicians that in these formative years, a good deal of the power and authority was concentrated in the Regents. As time goes on, there will be more power in the Board of Governors, and I think that is being done at the present time. It is certainly my intention, as far as my feeble powers will permit me, to continue that very definite trend. Eventually, of course, as it becomes standardized, it will be necessary that in a democratic institution, the activities, authority and powers that now rest largely in the Regents will be turned over somewhat to the Board of Governors, to the membership-at-large. That, of course, is a necessity in a democratic organization. However, at the present time, the concentration which still seems to me to be over-emphasized in the Board of Regents has to be gradually turned over to a certain extent to this body of Governors, and they, in turn, will turn it over to the membership-at-large.

"It is my general notion as to the function of the Governors as a body and individually, that individually and collectively they will have a much greater share in determining the activities and the policies of the College than they have had in the past. That seems to me definitely in order and it is taking place, and I shall do my best to give it a further push." (Applause)

Chairman Cocke then announced the appointment of one member of the Credentials Committee, whose term of service then expired. He reappointed Dr J Owsley Manier, Nashville, Tenn.

Dr Cocke then introduced Dr Thomas Parran, College Governor and Surgeon General of the United States Public Health Service. (Dr Parran's remarks at his request were omitted from these records.)

Chairman Cocke asked if there was any general business to bring before the meeting.

Dr Eugene H Drake, Governor for Maine, inquired if there were any special arrangements for Associates called to active military service, such as the extension of their Associate term beyond the five-year period prescribed in the By-Laws.

Chairman Cocke remarked that the matter was under consideration by the Board of Regents, and he felt assured that proper and adequate provision would be made for such men in some manner.

Dr William B Breed, as General Chairman, addressed the Board, pointing out that the Governors have a definite responsibility to the physicians who have been elected to Fellowship, and that the Board ought to urge as many as possible from their individual districts to be present at the Convocation, Wednesday evening. He also urged the Governors to attend the Banquet, and to aid the management by urging other physicians to obtain their tickets early.

Chairman Cocke brought up the matter of the meeting place for 1942, stating that while the Board of Regents have power for decision, the Board of Governors nevertheless is expected to make some sort of expression of preference. He asked the Executive Secretary to announce the cities from which invitations had come and the representatives from those cities to discuss their facilities. The Secretary announced the list of cities in alphabetical order, as follows: Buffalo, Milwaukee, Indianapolis, Kansas City, St Paul and San Francisco. He discussed the supporting invitations from the local County Medical Societies, the State Medical Societies, the Universities, civic bodies, etc.

Dr Nelson G Russell, on behalf of Buffalo, stated that they would be very happy to entertain the College, but had hesitated somewhat on account of limited facilities. He said, however, that he felt that Buffalo could furnish the proper number of clinics and hospital programs, and that the Buffalo Academy of Medicine and the University of Buffalo would join in the invitation.

Dr Karl H Doege, Alternate Governor for Wisconsin, stated that he knew nothing of the Milwaukee invitation, but expressed the opinion that housing facilities were adequate, but that distances to hospitals were rather long

Dr. Robert M Moore, Governor for Indiana, expressed the belief that Indianapolis would soon be ready for a College meeting, and he hoped that an invitation would be accepted in the not distant future

Dr A Comingo Griffith, Governor for Missouri, talked at greater length about the Kansas City invitation, extending the cordiality of the invitation and expressing his confidence that Kansas City would handle the meeting in a thoroughly successful manner

Dr Edgar V Allen, Governor for Minnesota, spoke on behalf of the St Paul invitation On behalf of the Governor of the State, the Mayor of St Paul and the entire medical profession of the State, he extended a very cordial invitation to meet in St Paul in 1942 On inquiry from one of the members, Dr. Allen explained that the Mayo Clinic is too far removed from St Paul for participation in the meeting He said the meeting could best be handled in St Paul and Minneapolis

Dr Ernest H Falconer spoke in regard to the invitation from San Francisco He expressed the desire to have the College return, but emphasized the importance of picking a year when there would be no disturbing influences to keep the members away, especially those from the eastern part of the country

Dr Cocke pointed out that the matter of physical facilities, opportunities for clinics, hospital programs, hotel accommodations, meeting halls and other considerations must be studied before an ultimate decision can be made by the Regents, regardless of suggestions or recommendations that may be made by the Governors

By motion regularly made, seconded and carried, it was agreed that the invitations from Kansas City and St Paul be considered by popular vote.

Chairman Cocke asked for a showing of hands There were nineteen votes for St Paul and twenty votes for Kansas City, which Dr. Cocke stated he would report to the Board of Regents

On motion by Dr A Comingo Griffith, seconded by several and unanimously carried, it was

Resolved, that the Board of Governors extend to those members of the College who had worked so hard on the preparation of the Boston meeting a cordial vote of thanks

After announcements by Dr Cocke, the meeting adjourned at 1:40 p m

Adjournment

Attest _____

ANNALS OF INTERNAL MEDICINE

AUTHOR INDEX

Volume 15, 1941

- AIRD, R. B. Experimental Exophthalmos and Associated Myopathy Induced by the Thyrotropic Hormone 564
- ALLEN, E. VAN N, Editor Specialties in Medical Practice *Rev* 149
- ARKIN, A, H POPPER and F A GOLDBERG Plasma Creatinine Determination as a Test of Low Grade Kidney Damage 700
- ARONSON, S F. Myasthenia Gravis, A Discussion, with Presentation of a Case Associated with a Thymoma *Case Rep.* 137
- ATTWOOD, C J, W H SARGENT and F TAYLOR Echinococcus Cyst of the Heart *Case Rep* 1109
- AVTRY, H Gastric and Duodenal Ulcers *Rev* 931
- BAGANZ, C N., H W STERLING and — Changes in the Cardiac Shadow Following Pharmacological "Shock" Therapy of Schizophrenia 459
- BAKER, A B, G R KAMMAN and — Syphilitic Pan-Meningitis (So-Called Chronic Hypertrophic Pachymeningitis) *Case Rep* 748
- BAUER, W, P S HENCH, —, E BOLAND, M H DAWSON, R H FREYBERG, W P HOLBROOK, J A KEY, L M LOCKIE and C McEWEN Rheumatism and Arthritis, Review of American and English Literature for 1940 (Eighth Rheumatism Review) 1002
- BERGER, A R, C E KOSSMANN and — Auricular Flutter of Eleven Years' Duration with Observations on Esophageal Electrocardiograms *Case Rep* 128
- BINGER, M W Edema *Edi* 617
- BIRKELO, C C, B H DOUGLAS and — Screening for Tuberculosis in a Civilian Population by Fluorography 853
- BLANKSTEIN, S S, N ENZER, E SIMONSON and — The State of Sensory and Motor Centers in Patients with Hypothyroidism 659
- BLOOMFIELD, J J Industrial Hygiene in the National Defense Program 165
- BOLAND, E, P S HENCH, W BAUER, —, M H DAWSON, R H FREYBERG, W P HOLBROOK, J A KEY, L M LOCKIE and C McEWEN Rheumatism and Arthritis, Review of American and English Literature for 1940 (Eighth Rheumatism Review) 1002
- BORTZ, E L The Responsibility of the American College of Physicians for Postgraduate Training 582
- BRAV, E A and H SIGMOND The Local and Regional Injection Treatment of Low Back Pain and Sciatica 840
- CAMIEL, M R and L LOEWE A Syndrome of Upper Esophageal Stenosis 63
- CATES, H B Acute Hepatitis of Alcoholism A Clinical and Laboratory Study 244
- CHAFEE, F H Sensitivity to Peanut Oil *Case Rep* 1116
- CHAMBERLAIN, F L, P D WHITE, — and S R KELSON Rupture of Aorta into the Pulmonary Artery with Long Survival *Case Rep* 589
- CLEMENT, F W Nitrous Oxide-Oxygen Anesthesia *Rev* 1119
- COHEN, M B A Manual of Allergy *Rev* 1119
- COMROE, B I Arthritis and Allied Conditions *Rev* 333
- COOPER, E L Familial Acholuric Jaundice Associated with Bone Changes 858
- COPE, Z The Early Diagnosis of the Acute Abdomen *Rev* 334
- CURTIS, A C and S S SOBIN The Solubility of Acetylsulfapyridine and Acetylsulfathiazole in the Urine 884
- DAMESHEK, W, K SINGER and — Symptomatic Hemolytic Anemia 544
- DAMMIN, G J Subacute Bacterial Endocarditis Caused by a Hitherto Un-

- described Gram Negative Coccus
Case Rep. 756
- DAWSON, M H, P S HENCH, W
BAUER, E BOLAND, —, R H FREY-
BERG, W P HOLBROOK, J A KEY,
L M LOCKIE and C MCEWEN
Rheumatism and Arthritis, Review of
American and English Literature for
1940 (Eighth Rheumatism Review) 1002
- DELF, M H and C J WEBER Ar-
senical Sensitivity and Vitamin C . 890
- DOUGLAS, B H and C C. BIRKELO
Screening for Tuberculosis in a Ci-
vilian Population by Fluorography 853
- DYER, R E Mass Immunization
against Typhus Fever 629
- EDELMAN, M H Thrombocytopenic
Purpura Associated with Discoid
Lupus Erythematosus and Renal
Glomerular Changes *Case Rep* 116
- EDSON, R C and A L STARKEY
A Roentgen Study of Cavities in
Pulmonary Tuberculosis, Cavity
Changes under Collapse and Non-
Collapse Measures 716
- ENSWORTH, H K, J LIEBMANN, M C
LOCKHART and N. PLUMMER Glu-
cose-Sulfapyridine, Experimental and
Clinical Studies 52
- ENZER, N, E SIMONSON and S S
BLANKSTEIN The State of Sensory
and Motor Centers in Patients with
Hypothyroidism 659
- ERF, L A and J H LAWRENCE
Clinical Studies with the Aid of
Radio-Phosphorus III The Ab-
sorption and Distribution of Radio-
Phosphorus in the Blood of, Its Ex-
cretion by, and Its Therapeutic Effect
on, Patients with Polycythemia 276
- ERF, L A, L W TUTTLE and J H.
LAWRENCE Clinical Studies with
the Aid of Radio-Phosphorus IV
The Retention in Blood, the Excre-
tion and the Therapeutic Effect of
Radio-Phosphorus on Patients with
Leukemia 487
- ERSHLER, I, G FAHR and — Studies
of the Factors Concerned in Edema
Formation II The Hydrostatic
Pressure in the Capillaries during
Edema Formation in Right Heart
Failure 798
- FAHR, G. and I ERSHLER Studies of
the Factors Concerned in Edema
Formation II The Hydrostatic
Pressure in the Capillaries during
Edema Formation in Right Heart
Failure 798
- FALCONER, E H and M E LEONARD
The Value of Sternal Marrow Aspira-
tion as a Method of Bone Marrow
Biopsy 446
- FEARON, W R An Introduction to
Biochemistry *Rev* 150
- FELSEN, J The Sigmoidoscopic Diag-
nosis of Periarthritis Nodosa 251
- FIESER, L. F The Chemistry of Vita-
min K 648
- FLAXMAN, N Hypertensive Heart Di-
sease of 10 to 20 Years' Duration,
Report of 11 Cases 821
- FREYBERG, R H, P S HENCH, W
BAUER, E BOLAND, M H DAWSON,
—, W P HOLBROOK, J A KEY, L
M LOCKIE and C MCEWEN Rheu-
matism and Arthritis, Review of
American and English Literature for
1940 (Eighth Rheumatism Review) 1002
- FRISCH, A W and A E PRICE Sputum
Studies in Pneumonia. The
Selection of Therapy 987
- GAMBILL, W D, I H PAGE, O M
HELMER, K G KOHLSTAEDT, G F
KEMPF, — and R D TAYLOR The
Blood Pressure Reducing Property of
Extracts of Kidneys in Hypertensive
Patients and Animals 347
- GARIS, R W Prerenal Uremia Due to
Papilloma of Rectum *Case Rep* 916
- GILMAN, A, L GOODMAN and — The
Pharmacological Basis of Thera-
peutics *Rev* 769
- GOLDBERG, F A, A ARKIN, H POPPER
and — Plasma Creatinine Deter-
mination as a Test of Low Grade
Kidney Damage 700
- GOODMAN, L and A GILMAN The
Pharmacological Basis of Thera-
peutics *Rev* 769
- HACHTEL, F. W, R B WRIGHT and —
Histoplasmosis of Darling *Case Rep* 309
- HALLIDAY, J L The Concept of Psy-
chosomatic Rheumatism 666

- HARRIS, A W and S A LEVINE Cerebral Embolism in Mitral Stenosis 637
- HECKER, A O Schizophrenia, A Neurobiologic Approach 678
- HELMER, O M, I H PAGE, —, K G KOHLSTAEDT, G F KEMPF, W D GAMBILL and R D TAYLOR The Blood Pressure Reducing Property of Extracts of Kidneys in Hypertensive Patients and Animals 347
- HENCH, P S, W BAUER, E BOLAND, M H DAWSON, R H FREYBERG, W P. HOLBROOK, J A KEY, L M LOCKIE and C McEWEN Rheumatism and Arthritis, Review of American and English Literature for 1940 (Eighth Rheumatism Review) 1002
- HERRICK, W W and T L TYSON The Medical Aspect of Ankylosing Spondylitis (Marie-Strumpell) 994
- HILF, H E and F K HICK Experiences in the Treatment of Subacute Bacterial Endocarditis with Sulfanilamide, Sulfapyridine and Sulfathiazole, A Review of Previously Reported Cured Cases with the Report of Fifteen Treated Cases Including One Cure and One Aborted Case 291
- HIGGINS, C C Hunner Ulcer of the Bladder (Review of 100 Cases) 708
- HIMMELSBACH, C K. The Morphine Abstinence Syndrome, Its Nature and Treatment 829
- HINES, L E and J T HUNT Pulmonary Infarction in Heart Disease 644
- HITCHINS, A P The Control of Infectious Diseases in Rapidly Mobilized Troops 172
- HOLBROOK, W P, P S HENCH, W BAUER, E BOLAND, M H DAWSON, R H FREYBERG, —, J A KEY, L M LOCKIE and C McEWEN Rheumatism and Arthritis, Review of American and English Literature for 1940 (Eighth Rheumatism Review) 1002
- HOLMES, G W and H E RUGGLES Roentgen Interpretation *Rev* 1120
- HOLMES, W H Bacillary and Rickettsial Infections *Rev* 769
- HORSFALL, F L, JR Influenza 811
- HOWARD, I, J C ZILLHARDT, — and W P MURPHY The Effect of a Vitamin B Complex on the Residual Neural Disturbances of Treated Pernicious Anemia 44
- HUNT, J T, L E HINES and — Pulmonary Infarction in Heart Disease. 644
- IRONS, E E The American Board of Internal Medicine as a Factor in Scholarship in American Medicine 304
- JOSLIN, E P, H F ROOT, P WHITE and A MARBLE The Treatment of Diabetes Mellitus *Rev* 931
- JULIANELLE, L A The Pneumonia of Friedländer's Bacillus 190
- JULIANELLE, L A, R G TORREY, — and H G McNAMEE The Sulfonamide Therapy of Staphylococcal Septicemia 431
- KAMMAN, G R and A B BAKER Syphilitic Pan-Meningitis (So-Called Chronic Hypertrophic Spinal Pachymeningitis) *Case Rep* 748
- KELSON, S R, P D WHITE, F L CHAMBERLAIN and — Rupture of Aorta into the Pulmonary Artery with Long Survival *Case Rep* 589
- KEMPF, G F, I H PAGE, O M HELMER, K G KOHLSTAEDT, —, W D GAMBILL and R D TAYLOR The Blood Pressure Reducing Property of Extracts of Kidneys in Hypertensive Patients and Animals 347
- KEY, J A, P S HENCH, W BAUER, E BOLAND, M H DAWSON, R H FREYBERG, W P HOLBROOK, —, L M LOCKIE and C McEWEN Rheumatism and Arthritis, Review of American and English Literature for 1940 (Eighth Rheumatism Review) 1002
- KINSELLA, R A Chemotherapy of Bacterial Endocarditis 982
- KLEIBER, E E Long Standing Productive Cough as Chief Clinical Manifestation in Mitral Stenosis, A Case Complicated by Thrombosis of Left Auricle *Case Rep* 899
- KLOTZ, B and B LIDMAN The Treatment of Acute Empyema, Treatment by Continuous Tidal Irrigation and Suction (Hart) 974
- KOHLSTAEDT, K G, I H PAGE, O M HELMER, —, G F KEMPF, W D GAMBILL and R D TAYLOR The

- Blood Pressure Reducing Property of
Extracts of Kidneys in Hypertensive
Patients and Animals 347
- KOPELOFF, N Bacteriology in Neuro-
psychiatry *Rev* 622
- KOSSMANN, C E and A R BERGER
Auricular Flutter of Eleven Years'
Duration with Observations on Eso-
phageal Electrocardiograms *Case
Rep* 128
- LAWRENCE, J H, L A ERF and —
Clinical Studies with the Aid of
Radio-Phosphorus III The Ab-
sorption and Distribution of Radio-
Phosphorus in the Blood of, Its Ex-
cretion by, and Its Therapeutic
Effect on, Patients with Polycythemia 276
- LAWRENCE, J H, L A ERF, L W
TUTTLE and — Clinical Studies
with the Aid of Radio-Phosphorus
IV The Retention in Blood, the Ex-
cretion and the Therapeutic Effect
of Radio-Phosphorus on Patients
with Leukemia 487
- LEACH, J E and F G MEDINGER
Micrococcus Tetragenus Meningitis,
Report of a Case and Review of the
Literature *Case Rep* 609
- LEONARD, M E, E H FALCONER and
— The Value of Sternal Marrow
Aspiration as a Method of Bone
Marrow Biopsy 446
- LEVINE, S A, A W HARRIS and —
Cerebral Embolism in Mitral Stenosis 637
- LEWEY, F H Neurological, Medical
and Biochemical Signs and Symp-
toms Indicating Chronic Industrial
Carbon Disulphide Absorption 869
- LIDMAN, B, B KLOTZ and — The
Treatment of Acute Empyema, Treat-
ment by Continuous Tidal Irrigation
and Suction (Hart) 974
- LIEBMANN, J, H K ENSWORTH, —,
M C LOCKHART and N PLUMMER
Glucose-Sulfapyridine, Experimental
and Clinical Studies 52
- LOCKHART, M C, H K ENSWORTH,
J LIEBMANN, — and N PLUMMER
Glucose-Sulfapyridine, Experimental
and Clinical Studies 52
- LOCKIE, L M, P S HENCH, W
BAUER, E BOLAND, M H DAWSON,
R H FREYBERG, W P HOLBROOK,
J A KEY, — and C McEWEN.
Rheumatism and Arthritis, Review
of American and English Literature
for 1940 (Eighth Rheumatism Re-
view) 1002
- LOEWE, L., M R CAMIEL and — A
Syndrome of Upper Esophageal Ste-
nosis 63
- MACLEAN, K, J C ZILLHARDT, — and
W P MURPHY The Effect of Thi-
amin on the Residual Neural Dis-
turbances of Treated Pernicious
Anemia 33
- MADIGAN, P. S The Recruit's First
Year 18
- MARBLE, A, E P JOSLIN, H F ROOT,
P WHITE and — The Treatment
of Diabetes Mellitus *Rev* 931
- MASTER, A M and J STRICKER
Myxedema Heart *Case Rep* 123
- MAY, L M Late Tularemic Septi-
cemia Recovery Following Adminis-
tration of Sulfanilamide Compounds
Case Rep 320
- McEWEN, C, P S HENCH, W BAUER,
E BOLAND, M H DAWSON, R H
FREYBERG, W P HOLBROOK, J A
KEY, L M LOCKIE and — Rheu-
matism and Arthritis, Review of
American and English Literature for
1940 (Eighth Rheumatism Review) 1002
- McGRAW, J J, M M STRUMIA and —
The Development of Plasma Prepara-
tions for Transfusions 80
- McNAMEE, H G, R G TORREY, L A
JULIANELLE and — The Sulfona-
mide Therapy of Staphylococcal Sep-
ticemia 431
- MEDINGER, F G, J E LEACH and —
Micrococcus Tetragenus Meningitis,
Report of a Case and Review of the
Literature *Case Rep* 609
- MILLER, T G Results from the
Management of Bleeding Gastric and
Duodenal Ulcer 390
- MOODIE, W The Doctor and the Diffi-
cult Child *Rev* 771
- MURPHY, W P, J C ZILLHARDT, K
MACLEAN and — The Effect of
Thiamin on the Residual Neural
Disturbances of Treated Pernicious
Anemia 33

- MURPHY, W P, J C ZILLHARDT, I HOWARD and — The Effect of a Vitamin B Complex on the Residual Neural Disturbances of Treated Pernicious Anemia 44
- NEELY, J M Idiopathic Cardiac Enlargement Occurring in Infants and Children 727
- NICKLAS, E W, W M YATER and — Cold Allergy *Case Rep* 743
- PAGE, I H, O M HELMER, K G KOHLSTAEDT, G F KEMPF, W D GAMBILL and R D TAYLOR The Blood Pressure Reducing Property of Extracts of Kidneys in Hypertensive Patients and Animals 347
- PARDEE, H E B Clinical Aspects of the Electrocardiogram *Rev* 620
- PLUMMER, N, H K ENSWORTH, J LIEBMANN, M C LOCKHART and — Glucose-Sulfapyridine, Experimental and Clinical Studies 52
- POLLACK, H Modern Diabetic Care *Rev* 333
- POMERENZE, H, P STARR and — Therapeutic Studies in Hyperthyroidism 226
- POPPLER, H, A ARKIN, — and F A GOLDBERG Plasma Creatinine Determination as a Test of Low Grade Kidney Damage 700
- PREVOST, J V, J J WHITE and — Weil's Disease, Report of Three Cases, Including the Morbid Anatomy of One Case, and a Brief Review of the Pertinent Literature 207
- PRICE, A E, A W FRISCH and — Sputum Studies in Pneumonia The Selection of Therapy 987
- RATHBUN, H K and J M WAGHELS-STEIN Weil's Disease, Report of Six Cases 395
- RAVIN, A Tachycardia and Sensitivity to Heat as Indications for Basal Metabolic Rate Determination 478
- REID, W D Manual of Cardiology *Rev* 149
- RICE, G D, J SOLOVAY, — and H U SOLOVAY Electrocardiographic Changes in Stab and Gunshot Wounds of the Heart, with Review of the Literature 465
- RICHARDS, G G Unilateral Renal Tuberculosis Associated with Hypertension *Case Rep* 324
- RINKOFF, S S and M SPRING Toxic Depression of the Myeloid Elements Following Therapy with the Sulfonamides, Report of 8 Cases 89
- ROOT, H F, E P JOSLIN, —, P WHITE and A MARBLE The Treatment of Diabetes Mellitus *Rev* 931
- RUGGLES, H E, G W HOLMES and — Roentgen Interpretation *Rev* 1120
- SALTER, W T The Endocrine Function of Iodine *Rev* 334
- SARGENT, W H, C J ATTWOOD, — and F TAYLOR Echinococcus Cyst of the Heart *Case Rep* 1109
- SCHAEFER, G, H C WILLIAMSON and — Obstetrics *Rev* 931
- SEBRELL, W H The Clinical Symptoms and Signs of Vitamin B Complex Deficiency 953
- SEGAL, J Pulmonary Tuberculosis (A Synopsis) *Rev* 932
- SELLING, L S Some Problems Confronting the Physician in the Examination of Automobile Drivers 265
- SIGMOND, H, E A BRAV and — The Local and Regional Injection Treatment of Low Back Pain and Sciatica 840
- SIMONSON, E, N ENZER, — and S S BLANKSTEIN The State of Sensory and Motor Centers in Patients with Hypothyroidism 659
- SIMPSON, W M The Diagnosis and Management of Brucellosis 408
- SINGER, K and W DAMESHEK Symptomatic Hemolytic Anemia 544
- SLADEN, F J The Responsibility of the Hospital Staff in Graduate Medical Education 108
- SNELL, G D, Editor Biology of the Laboratory Mouse *Rev* 1121
- SOBIN, S S, A C CURTIS and — The Solubility of Acetylsulfapyridine and Acetylsulfathiazole in the Urine 884
- SOLOVAY, J, G D RICE and H U SOLOVAY Electrocardiographic Changes in Stab and Gunshot Wounds of the Heart, with Review of the Literature 465

- SPRING, M, S S RINKOFF and —
Toxic Depression of the Myeloid
Elements Following Therapy with
the Sulfonamides, Report of 8 Cases 89
- STADIE, W C Fat Metabolism in
Diabetes Mellitus 783
- STANDER, H J Williams' Obstetrics
Rev 620
- STARKEY, A L, R C EDSON and —
A Roentgen Study of Cavities in Pul-
monary Tuberculosis, Cavity Changes
under Collapse and Non-Collapse
Measures 716
- STARR, P and H POMERENZE Thera-
peutic Studies in Hyperthyroidism 226
- STEPHENSON, C S Special Medical
Service in the Defense Program 1
- STERLING, H W and C N BAGANZ
Changes in the Cardiac Shadow
Following Pharmacological "Shock"
Therapy of Schizophrenia 459
- STRICKER, J, A M MASTER and —
Myxedema Heart *Case Rep* 123
- STROUD, W D and J A WAGNER.
Silent or Atypical Coronary Occlusion 25
- STRUMIA, M M and J J MCGRAW
The Development of Plasma Prepara-
tions for Transfusions 8
- SULZBERGER, M B and J WOLF.
Dermatologic Therapy in General
Practice *Rev* 1120
- SWEANY, H C, F TICE and —
A Fatal Case of Besnier-Boeck-
Schaumann's Disease with Autopsy
Findings *Case Rep* 597
- SYDENSTRICKER, V P The Syndrome
of Multiple Vitamin Deficiency 45
- TAYLOR, F, C J ATTWOOD, W H
SARGENT and — Echinococcus Cyst
of the Heart *Case Rep* 1109
- TAYLOR, R D, I H PAGE, O M
HELMER, K G KOHLSTAEDT, G F
KEMPF, W D GAMBILL and — The
Blood Pressure Reducing Property of
Extracts of Kidneys in Hypertensive
Patients and Animals 347
- TICE, F and H C SWEANY A Fatal
Case of Besnier-Boeck-Schaumann's
Disease with Autopsy Findings *Case
Rep* 597
- TOBIAS, N Essentials of Dermatology
Rev 151
- TOOMEY, J A Scarlet Fever Immun-
ization 959
- TORREY, R G, L A JULIANELLE and
H G MCNAMEE The Sulfonamide
Therapy of Staphylococcal Septi-
cemia 431
- TUTTLE, L W, L A ERF, — and J H
LAWRENCE Clinical Studies with
the Aid of Radio-Phosphorus IV
The Retention in Blood, the Excre-
tion and the Therapeutic Effect of
Radio-Phosphorus on Patients with
Leukemia 487
- TYSON, T L, W W HERRICK and —
The Medical Aspect of Ankylosing
Spondylitis (Marie-Strumpell) 994
- WAGHELSTEIN, J M, H K RATHBUN
and — Weil's Disease, Report of
Six Cases 395
- WAGNER, J A, W D STROUD and —
Silent or Atypical Coronary Occlusion 25
- WEBER, C J, M H DELP and —
Arsenical Sensitivity and Vitamin C 890
- WHITE, J J and J V PREVOST Weil's
Disease, Report of Three Cases, In-
cluding the Morbid Anatomy of One
Case, and a Brief Review of the
Pertinent Literature 207
- WHITE, P, E P JOSLIN, H F ROOT,
— and A MARBLE The Treatment
of Diabetes Mellitus *Rev* 931
- WHITE, P D, F L CHAMBERLAIN and
S R KELSON Rupture of Aorta
into the Pulmonary Artery with Long
Survival *Case Rep* 589
- WIGGERS, C J The Mechanisms of
Peripheral Circulatory Failure 178
- WILE, U J The Principles Underlying
the Treatment of Cardiovascular
Syphilis 817
- WILLIAMSON, H C and G SCHAEFER
Obstetrics *Rev* 931
- WILLIUS, F A Cardiac Clinics *Rev* 770
- WOLF, J, M B SULZBERGER and —
Dermatologic Therapy in General
Practice *Rev* 1120
- WRIGHT, R B and F W HACHTEL
Histoplasmosis of Darling *Case Rep* 309
- YATER, W M and E W NICKLAS
Cold Allergy *Case Rep* 743
- YOUNG, R H Association of Postural
Hypotension with Sympathetic Ner-

vious System Dysfunction, Case Report, with Review of Neurologic Features Associated with Postural Hypotension <i>Case Rep</i>	910	ZILLHARDT, J C, I HOWARD and W P MURPHY The Effect of a Vitamin B Complex on the Residual Neural Disturbances of Treated Pernicious Anemia	44
ZILLHARDT, J C, K MACLEAN and W P MURPHY The Effect of Thiamin on the Residual Neural Disturbances of Treated Pernicious Anemia	33	ZONDEK, B Clinical and Experimental Investigations on the Genital Functions and Their Hormonal Regulation <i>Rev</i>	621

ANNALS OF INTERNAL MEDICINE

SUBJECT INDEX

Volume 15, 1941

- A**BDOMEN, The Early Diagnosis of the Acute— Z COPE *Rev* 334
- Acetylsulfapyridine and Acetylsulfathiazole in the Urine, The Solubility of— A C CURTIS and S S SOBIN 884
- Alcoholism, Acute Hepatitis of— A Clinical and Laboratory Study H B CATES 244
- Allergy, A Manual of— M B COHEN *Rev* 1119
- Allergy, Cold— Report of an Unusual Case W M YATER and E W NICKLAS *Case Rep* 743
- American Board of Internal Medicine as a Factor in Scholarship in American Medicine, The— E E IRONS 304
- American College of Physicians, The Responsibility of the—for Postgraduate Training E L BORTZ 582
- Anemia, Symptomatic Hemolytic— K SINGER and W DAMESHEK 544
- Anesthesia, Nitrous Oxide-Oxygen— F W CLEMENT *Rev* 1119
- Ankylosing Spondylitis, The Medical Aspect of—(Marie-Strumpell) W W HERRICK and T L TYSON 994
- Aorta, Rupture of—into the Pulmonary Artery with Long Survival P D WHITE, F L CHAMBERLAIN and S R KELSON *Case Rep* 589
- Arsenical Sensitivity and Vitamin C M H DELP and C J WEBER 890
- Arthritis and Allied Conditions B I COMROE *Rev* 333
- Arthritis, Rheumatism and—, Review of American and English Literature for 1940 (Eighth Rheumatism Review) P S HENCH, W BAUER, E BOLAND, M H DAWSON, R H FREYBERG, W. P HOLBROOK, J A KEY, L M LOCKIE and C MCEWEN 1002
- Auricular Flutter of Eleven Years' Duration with Observations on Esophageal Electrocardiograms C E KOSSMANN and A R BERGER *Case Rep* 128
- Automobile Drivers, Some Problems Confronting the Physician in the Examination of— L S SELLING 265
- B**ACILLARY and Rickettsial Infections W H HOLMES *Rev* 769
- Bacteriology in Neuropsychiatry N KOPELOFF *Rev* 622
- Basal Metabolic Rate Determination, Tachycardia and Sensitivity to Heat as Indications for— A RAVIN 478
- Besnier-Boeck-Schaumann's Disease, A Fatal Case of—with Autopsy Findings F TICE and H C SWEANY *Case Rep* 597
- Biochemistry, An Introduction to— W R FEARON *Rev* 150
- Biology of the Laboratory Mouse G D SNELL, Editor. *Rev.* 1121
- Bladder, Hunner Ulcer of the—(Review of 100 Cases) C C HIGGINS 708
- Bleeding Gastric and Duodenal Ulcer, Results from the Management of— T G MILLER 390
- Blood Pressure Reducing Property of Extracts of Kidneys in Hypertensive Patients and Animals, The— I H PAGE, O M HELMER, K G KOHLSTAEDT, G F KEMPF, W D GAMBILL and R D. TAYLOR 347
- Bone Marrow Biopsy, The Value of Sternal Marrow Aspiration as a Method of— E H FALCONER and M E LEONARD 446
- Brucellosis, The Diagnosis and Management of— W M SIMPSON 408
- C**ARBON Disulphide Absorption, Neurological, Medical and Biochemical Signs and Symptoms Indicating Chronic Industrial— F H LEWEY 869
- Cardiac Clinics F A WILLIUS *Rev* 770
- Cardiac Enlargement, Idiopathic—Occurring in Infants and Children J M NEELY 727

- Cardiac Shadow, Changes in the—
Following Pharmacological "Shock"
Therapy of Schizophrenia H W
STIRLING and C. N BAGANZ 459
- Cardiology, Manual of— W D REID
Rev 149
- Cardiovascular Syphilis, The Principles
Underlying the Treatment of— U
J WILC 817
- Cerebral Embolism in Mitral Stenosis
A W HARRIS and S A LEVINE 637
- Chemistry of Vitamin K, The— L F
FISHER 648
- Chemotherapy of Bacterial Endocar-
ditis R A KINSELLA 982
- Child, The Doctor and the Difficult—
W MOODIE Rev 771
- Circulatory Failure, The Mechanisms of
Peripheral— C J WIGGERS 178
- Cold Allergy Report of an Unusual
Case W M YATER and E W
NICKLAS Case Rep 743
- Coronary Occlusion, Silent or Atypical
— W D STROUD and J A WAGNER 25
- D**AYS Ahead, The—
Edit 1118
- Defense The Control of Infectious
Diseases in Rapidly Mobilized Troops
A P HITCHENS 172
- Defense Program, Industrial Hygiene in
the National— J J BLOOMFIELD 165
- Defense Program, Special Medical Serv-
ice in the— C S STEPHENSON 1
- Dermatologic Therapy in General Prac-
tice M B SULZBERGER and J
WOLF Rev 1120
- Dermatology, Essentials of— N
TOBIAS Rev 151
- Diabetes Mellitus, Fat Metabolism in
— W C STADIE 783
- Diabetes Mellitus, The Treatment of—
E P JOSLIN, H F ROOT, P WHITE
and A MARBLE Rev 931
- Diabetic Care, Modern— H POL-
LACK Rev 333
- Doctor and the Difficult Child, The—
W MOODIE Rev 771
- Duodenal Ulcer, Results from the Man-
agement of Bleeding Gastric and—
T G MILLER 390
- Duodenal Ulcers, Gastric and— H
AVERY Rev 931
- E**CHINOCOCCUS Cyst of the Heart
C J ATTWOOD, W H SARGENT
and F TAYLOR Case Rep 1109
- Edema M W BINGER Edit 617
- Edema Formation, Studies of the Fac-
tors Concerned in— II The Hy-
drostatic Pressure in the Capillaries
during Edema Formation in Right
Heart Failure G FAHR and I
ERSHLER 798
- Electrocardiogram, Clinical Aspects of
the— H E B PARDEE Rev 620
- Electrocardiograms, Auricular Flutter
of Eleven Years' Duration with Ob-
servations on Esophageal— C E
KOSSMANN and A R BERGER Case
Rep 128
- Electrocardiographic Changes in Stab
and Gunshot Wounds of the Heart,
with Review of the Literature J
SOLOVAY, G D RICE and H U
SOLOVAY 465
- Embolism, Cerebral—in Mitral Stenosis
A W HARRIS and S A LEVINE 637
- Empyema, The Treatment of Acute—,
Treatment by Continuous Tidal Irri-
gation and Suction (Hart) B KLOTZ
and B LIDMAN 974
- Endocarditis, Chemotherapy of Bac-
terial— F A KINSELLA 982
- Endocarditis, Experiences in the Treat-
ment of Subacute Bacterial—, A Re-
view of Previously Reported Cured
Cases with the Report of Fifteen
Treated Cases Including One Cure
and One Aborted Case H E HEYER
and F K HICK 291
- Endocarditis, Subacute Bacterial—
Caused by a Hitherto Undescribed
Gram Negative Coccus G J DAM-
MIN Case Rep 756
- Endocrine Function of Iodine, The—
W T SALTER Rev 334
- Esophagus A Syndrome of Upper
Esophageal Stenosis M R CAMIEL
and L LOEWE 63
- Exophthalmos, Experimental—and As-
sociated Myopathy Induced by the
Thyrotropic Hormone R B AIRD 564
- F**AMILIAL Acholuric Jaundice As-
sociated with Bone Changes E.
L COOPER 858

- Fat Metabolism in Diabetes Mellitus
W C STADIE 783
- Friedlander's Bacillus, The Pneumonia
of— L A JULIANELLE 190
- G**ASTRIC and Duodenal Ulcers
H AVERY *Rev* 931
- Genital Functions and Their Hormonal
Regulation, Clinical and Experimental
Investigations on the— B ZONDEK
Rev 621
- Glucose-Sulfapyridine, Experimental
and Clinical Studies H K ENS-
WORTH, J LIEBMANN, M C LOCK-
HART and N PLUMMER 52
- H**EART, Echinococcus Cyst of the
— C J ATTWOOD, W H SAR-
GENT and F TAYLOR *Case Rep* 1109
- Heart, Electrocardiographic Changes in
Stab and Gunshot Wounds of the—
with Review of the Literature J
SOLOVAY, G D RICE and H U SOLO-
VAY 465
- Heart Disease, Hypertensive—of 10 to
20 Years' Duration, Report of 11
Cases N FLAXMAN 821
- Heart Failure, The Hydrostatic Pres-
sure in the Capillaries during Edema
Formation in Right— Studies of the
Factors Concerned in Edema Forma-
tion II— G FAHR and I ERSHLER 798
- Hemolytic Anemia, Symptomatic—
K SINGER and W DAMESHEK 544
- Hepatitis of Alcoholism, Acute— A
Clinical and Laboratory Study H
B CATES 244
- Histoplasmosis of Darling R. B.
WRIGHT and F W HACHTEL *Case
Rep* 309
- Hormone, Experimental Exophthalmos
and Associated Myopathy Induced by
the Thyrotropic— R B. AIRD 564
- Hospital Staff, The Responsibility of
the—in Graduate Medical Education
F J SLADEN 108
- Hunner Ulcer of the Bladder (Review
of 100 Cases) C C HIGGINS 708
- Hypertension, Unilateral Renal Tuber-
culosis Associated with— G G
RICHARDS *Case Rep* 324
- Hypertensive Heart Disease of 10 to 20
Years' Duration, Report of 11 Cases
N FLAXMAN 821
- Hyperthyroidism, Therapeutic Studies
in— P STARR and H POMERENZE 226
- Hypotension, Case Report, with Re-
view of Neurologic Features Asso-
ciated with Postural— Association
of Postural Hypotension with Sym-
pathetic Nervous System Dysfunc-
tion,— R H YOUNG *Case Rep* 910
- Hypothyroidism, The State of Sensory
and Motor Centers in Patients with
— N ENZER, E SIMONSON and
S S BLANKSTEIN 659
- I**DIOPATHIC Cardiac Enlargement
Occurring in Infants and Children
J M NEELY 727
- Immunity to Malaria *Edit* 146
- Industrial Hygiene in the National De-
fense Program J J BLOOMFIELD 165
- Infantile Paralysis—A Symposium De-
livered at Vanderbilt University,
April, 1941 *Rev* 770
- Infarction, Pulmonary—in Heart Dis-
ease L E HINES and J T HUNT 644
- Infectious Diseases, The Control of—in
Rapidly Mobilized Troops A P
HITCHENS 172
- Influenza F L HORSFALL, JR 811
- Iodine, The Endocrine Function of—
W T SALTER *Rev* 334
- Isoagglutinins, The Significance of Hu-
man Atypical— *Edit* 927
- J**AUNDICE, Familial Acholuric—As-
sociated with Bone Changes E
L COOPER 858
- K**IDNEY Damage, Plasma Creat-
inine Determination as a Test of
Low Grade— A ARKIN, H POPPER
and F A GOLDBERG 700
- Kidneys, The Blood Pressure Reducing
Property of Extracts of—in Hyper-
tensive Patients and Animals I H
PAGE, O M HELMER, K G KOHL-
STAEDT, G F KEMPF, W D GAMBILL
and R D TAYLOR 347
- L**EUKEMIA, The Retention in
Blood, the Excretion and the
Therapeutic Effect of Radio-Phos-
phorus on Patients with— Clinical
Studies with the Aid of Radio-Phos-

- phorus IV— L A ERR, L W
TUTTLE and J H LAWRENCE 487
- Local and Regional Injection Treatment
of Low Back Pain and Sciatica, The
— E A BRAV and H SIGMOND 840
- Lupus Erythematosus and Renal Glo-
merular Changes, Thrombocytopenic
Purpura Associated with Discoid—
M H EDELMAN *Case Rep* 116
- M**ALARIA, Immunity to—
Edit 146
- Mass Immunization against Typhus
Fever R E DYER 629
- Medical Education, The Responsibility
of the Hospital Staff in Graduate—
F J SLADEN 108
- Medical Practice, Specialties in— E
VAN N ALLEN, Editor *Rev* 149
- Medicine, Landmarks in— *Rev* 334
- Medicine, The American Board of
Internal Medicine as a Factor in
Scholarship in American— E E
IRONS 304
- Meningitis, Micrococcus Tetragenus—,
Report of a Case and Review of the
Literature J E LEACH and F G
MEDINGER *Case Rep* 609
- Meningitis, Syphilitic Pan—(So-Called
Chronic Hypertrophic Spinal Pachy-
meningitis) G R KAMMAN and
A B BAKER *Case Rep* 748
- Micrococcus Tetragenus Meningitis,
Report of a Case and Review of the
Literature J E LEACH and F G
MEDINGER *Case Rep* 609
- Mitral Stenosis, Cerebral Embolism in
— A W HARRIS and S A LEVINE 637
- Mitral Stenosis, Long Standing Produc-
tive Cough as Chief Clinical Mani-
festation in—, A Case Complicated
by Thrombosis of Left Auricle E E
KLEIBER *Case Rep* 899
- Morphine Abstinence Syndrome, The—,
Its Nature and Treatment C K
HIMMELSBACH 829
- Mouse, Biology of the Laboratory—
G D SNELL, Editor *Rev* 1121
- Myasthenia Gravis, A Discussion, with
Presentation of a Case Associated
with a Thymoma S F ARONSON
Case Rep 137
- Myeloid Elements, Toxic Depression of
the—Following Therapy with the

- Sulfonamides, Report of 8 Cases
S S RINKOFF and M SPRING 89
- Myxedema Heart A M MASTER and
J STRICKER *Case Rep* 123

- N**EUROLOGICAL, Medical and
Biochemical Signs and Symptoms
Indicating Chronic Industrial Car-
bon Disulphide Absorption F H
LEWEY 869
- Neuropsychiatry, Bacteriology in—
N KOPELOFF *Rev* 622
- Nitrous Oxide-Oxygen Anesthesia F
W CLEMENT *Rev* 1119

OBITUARIES

- Albee, George Macdonald 1131
- Baird, Raleigh William 943
- Bishop, Louis Faugeres, Sr 1132
- Campbell, Edward Everett 1129
- Cheney, William Fitch 162
- Clow, Fred Ellsworth 345
- Compton, Marion Lee 942
- DeWitt, Alexander S 345
- Dunham, John Dudley 163
- Fairbanks, Warren Horace 941
- Fordham, George 1130
- Friedenwald, Julius 343
- Hollingsworth, Edward West 160
- Joachim, Henry 779
- Jones, Austin B 941
- Jones, Clement L 1129
- Kaufman, Isadore 780
- Kieser, Henry Samuel 344
- Kinlaw, William Bernard 780
- Krause, Allen Kramer 778
- Moor, F Clifton 345
- Olmsted, George Kingsley 942
- Riley, William Henry 1134
- Stem, Leon Thayer 161
- Stephens, Doran J 346
- Strietmann, William Hurley 782
- Syman, Louis Lawrence 1134
- Talley, James Ely 343
- Walsh, William Henry 159
- Wiener, Joseph 1135
- Wilson, William Henry 781
- Obstetrics H C WILLIAMSON and G
SCHAEFER *Rev* 931
- Obstetrics, Williams'— H J
STANDER *Rev* 620

- P**ANCREATITIS, The Association of Acute—with Diabetes Mellitus *Edut* 766
- Peanut Oil, Sensitivity to—with the Report of a Case F H CHAFEE *Case Rep* 1116
- Periarteritis Nodosa, The Sigmoidoscopic Diagnosis of— J FELSEN 251
- Peripheral Circulatory Failure, The Mechanisms of— C J WIGGERS 178
- Pernicious Anemia, The Effect of a Vitamin B Complex on the Residual Neural Disturbances of Treated— J C ZILLHARDT, I HOWARD and W P MURPHY 44
- Pernicious Anemia, The Effect of Thiamin on the Residual Neural Disturbances of Treated— J C ZILLHARDT, K MACLEAN and W P MURPHY 33
- Pharmacological Basis of Therapeutics, The— L GOODMAN and A GILMAN *Rev* 769
- Plasma Creatinine Determination as a Test of Low Grade Kidney Damage A ARKIN, H POPPER and F A GOLDBERG 700
- Plasma Preparations, The Development of—for Transfusions M. M STRUMIA and J J MCGRAW 80
- Pneumonia of Friedlander's Bacillus, The— L A JULIANELLE 190
- Pneumonia, Sputum Studies in— The Selection of Therapy A W FRISCH and A E PRICE 987
- Poliomyelitis, The Pathway of Infection in— *Edut* 329
- Polycythemia, The Absorption and Distribution of Radio-Phosphorus in the Blood of, Its Excretion by, and Its Therapeutic Effect on, Patients with — Clinical Studies with the Aid of Radio-Phosphorus III — L A ERF and J H LAWRENCE 276
- Postgraduate Training, The Responsibility of the American College of Physicians for— E L BORTZ 582
- Postural Hypotension, Association of—with Sympathetic Nervous System Dysfunction, Case Report, with Review of Neurologic Features Associated with Postural Hypotension R H YOUNG *Case Rep* 910
- Prerenal Uremia Due to Papilloma of Rectum R W GARIS *Case Rep* 916
- Psychosomatic Rheumatism, The Concept of— J L HALLIDAY 666
- Pulmonary Artery, Rupture of Aorta into the—with Long Survival P D WHITE, F L. CHAMBERLAIN and S R KELSON *Case Rep* 589
- Pulmonary Infarction in Heart Disease L E HINES and J T HUNT 644
- Pulmonary Tuberculosis (A Synopsis) J SEGAL *Rev* 932
- Purpura, Thrombocytopenic—Associated with Discoid Lupus Erythematosus and Renal Glomerular Changes M H EDELMAN *Case Rep* 116
- R**ADIO-PHOSPHORUS, Clinical Studies with the Aid of— III The Absorption and Distribution of Radio-Phosphorus in the Blood of, Its Excretion by, and Its Therapeutic Effect on, Patients with Polycythemia L A ERF and J H LAWRENCE 276
- Radio-Phosphorus, Clinical Studies with the Aid of— IV The Retention in Blood, the Excretion and the Therapeutic Effect of Radio-Phosphorus on Patients with Leukemia L A ERF, L W TUTTLE and J H LAWRENCE 487
- Recruit's First Year, The— P S MADIGAN 18
- Renal Tuberculosis, Unilateral—Associated with Hypertension G G RICHARDS *Case Rep* 324
- Rheumatism and Arthritis, Review of American and English Literature for 1940 (Eighth Rheumatism Review) P S HENCH, W BAUER, E BOLAND, M H DAWSON, R H FREYBERG, W P HOLBROOK, J A KEY, L M LOCKIE and C McEWEN 1002
- Rheumatism, The Concept of Psychosomatic— J L HALLIDAY 666
- Rickettsial Infections, Bacillary and— W H HOLMES *Rev* 769
- Roentgen Interpretation G W HOLMES and H E RUGGLES *Rev* 1120
- Roentgen Study of Cavities in Pulmonary Tuberculosis, A—; Cavity Changes Under Collapse and Non-Collapse Measures R C EDSON and A L. STARKEY 716

- Rupture of Aorta into the Pulmonary Artery with Long Survival P D WHITE, F L CHAMBERLAIN and S R KELSON *Case Rep* 589
- S** CARLET Fever Immunization J A TOOMEY 959
- Schizophrenia, A Neurobiologic Approach A O HECKER 678
- Schizophrenia, Changes in the Cardiac Shadow Following Pharmacological "Shock" Therapy of— H W STERLING and C N BAGANZ 459
- Sciatica, The Local and Regional Injection Treatment of Low Back Pain and— E A BRAV and H SIGMOND 840
- Screening for Tuberculosis in a Civilian Population by Fluorography B H DOUGLAS and C C BIRKELO 853
- Sensitivity to Peanut Oil with the Report of a Case F H CHAFFEE *Case Rep* 1116
- "Shock" Therapy of Schizophrenia, Changes in the Cardiac Shadow Following Pharmacological— H W STERLING and C N BAGANZ 459
- Sigmoidoscopic Diagnosis of Periarthritis Nodosa, The— J FELSEN 251
- Significance of Human Atypical Isoagglutinins, The— *Edt* 927
- Silent or Atypical Coronary Occlusion W D STROUD and J A WAGNER 25
- Specialties in Medical Practice E VAN N ALLEN, Editor *Rev* 149
- Spondylitis, The Medical Aspect of Ankylosing—(Marie-Strümpell) W W HERRICK and T L TYSON 994
- Sputum Studies in Pneumonia The Selection of Therapy A W FRISCH and A E PRICE 987
- Staphylococcal Septicemia, The Sulfonamide Therapy of— R G TORREY, L A JULIANELLE and H G MCNAMEE 431
- Sternal Marrow Aspiration as a Method of Bone Marrow Biopsy, The Value of— E H FALCONER and M E LEONARD 446
- Subacute Bacterial Endocarditis Caused by a Hitherto Undescribed Gram Negative Coccus G J DAMMIN *Case Rep* 756
- Subacute Bacterial Endocarditis, Experiences in the Treatment of—, A Review of Previously Reported Cured Cases with the Report of Fifteen Treated Cases Including One Cure and One Aborted Case H E HEYER and F K HICK 291
- Sulfanilamide Compounds, Recovery Following Administration of— Late Tularemic Septicemia,— L M MAY *Case Rep* 320
- Sulfapyridine, Glucose—, Experimental and Clinical Studies H K ENSWORTH, J LIEBMANN, M C LOCKHART and N PLUMMER 52
- Sulfonamide Therapy of Staphylococcal Septicemia, The— R G TORREY, L A JULIANELLE and H G MCNAMEE 431
- Sulfonamides, Toxic Depression of the Myeloid Elements Following Therapy with the—, Report of 8 Cases S S RINKOFF and M SPRING 89
- Symptomatic Hemolytic Anemia K SINGER and W DAMESHEK 544
- Syndrome of Multiple Vitamin Deficiency, The— V P SYDENSTRICKER 45
- Syndrome of Upper Esophageal Stenosis, A— M R CAMIEL and L LOEWE 63
- Syphilis, The Principles Underlying the Treatment of Cardiovascular— U J WILE 817
- Syphilitic Pan-Meningitis (So-Called Chronic Hypertrophic Spinal Pachymeningitis) G R KAMMAN and A B BAKER *Case Rep* 748
- T** ACHYCARDIA and Sensitivity to Heat as Indications for Basal Metabolic Rate Determination A RAVIN 478
- Therapeutic Studies in Hyperthyroidism P STARR and H POMERENZE 226
- Thiamin, The Effect of—on the Residual Neural Disturbances of Treated Pernicious Anemia J C ZILLHARDT, K MACLEAN and W P MURPHY 33
- Thrombocytopenic Purpura Associated with Discoid Lupus Erythematosus and Renal Glomerular Changes M H EDELMAN *Case Rep* 116
- Thymoma, A Discussion, with Presentation of a Case Associated with a— Myasthenia Gravis,— S F ARONSON *Case Rep* 137

- Thyrotropic Hormone, Experimental Exophthalmos and Associated Myopathy Induced by the— R B AIRD
- Toxic Depression of the Myeloid Elements Following Therapy with the Sulfonamides, Report of 8 Cases S S RINKOFF and M SPRING
- Transfusions, The Development of Plasma Preparations for— M M STRUMIA and J J MCGRAW
- Tuberculosis, A Roentgen Study of Cavities in Pulmonary—, Cavity Changes under Collapse and Non-Collapse Measures R C EDSON and A L STARKEY
- Tuberculosis, Pulmonary—(A Synopsis) J SEGAL *Rev*
- Tuberculosis, Screening for—in a Civilian Population by Fluorography B. H DOUGLAS and C C BIRKELO
- Tularemic Septicemia, Late— Recovery Following Administration of Sulfanilamide Compounds L M MAY *Case Rep*
- Typhus Fever, Mass Immunization against— R E DYER
- U**NILATERAL Renal Tuberculosis Associated with Hypertension G G RICHARDS *Case Rep*
- Uremia, Prerenal—Due to Papilloma of Rectum R W GARIS *Case Rep*
- V**ITAMIN B Complex Deficiency, The Clinical Symptoms and Signs of— W H SEBRELL
- Vitamin B Complex, The Effect of a— on the Residual Neural Disturbances of Treated Pernicious Anemia J C ZILLHARDT, I HOWARD and W P MURPHY
- Vitamin C, Arsenical Sensitivity and— M H DELP and C J WEBER
- Vitamin Deficiency, The Syndrome of Multiple— V P SYDENSTRICKER
- Vitamin K, The Chemistry of— L F. FIESER
- W**EIL'S Disease, Report of Six Cases H K, RATHBUN and J M WAGHELSTEIN
- Weil's Disease, Report of Three Cases, Including the Morbid Anatomy of One Case, and a Brief Review of the Pertinent Literature J J WHITE and J V PREVOST
- Williams' Obstetrics H J STANDER *Rev*

916

564

953

89

80

44

890

716

45

932

648

853

395

320

629

207

324

620

The following *physical* and *laboratory* signs were found Aorta tortuous, blood pressure 150 mm Hg systolic and 100 mm diastolic, blood picture normal, serum cholesterol 266 mg per cent, urine normal; CS₂ excretion in urine 25–50 γ per cent, or 0.3–0.6 mg in 24 hours

Neurological examination Slight pallor of optic discs, marked decrease of pupillary reflexes to light (right, 19.4 per cent, left, 24.6 per cent), slight decrease of corneal reflexes (0.43 and 0.5 mg/mm²), short choreic movements of the extremities, and continual twitching movements in the muscles of the arms and legs were present A strongly positive Noica sign was elicited in both arms The left arm did not swing in walking A positive reaction of convergence was observed in the left arm in testing postural reflexes Knee jerks were hypoactive, Achilles reflexes absent bilaterally There was decrease of pain sensitivity in the left arm and leg, and tenderness to pressure on left radial and ulnar nerves The electrical irritability of the flexor muscles of the fingers was mildly decreased (6.2V μ C), of the peroneal muscles moderately decreased (6.4V μ C) There was a reversal of the polar formula in the former.

Diagnosis Thalamic syndrome without involvement of the pyramidal tracts, and mild polyneuropathy

A syndrome such as cited above might well be expected following apoplexy, but the most intensive inquiry failed to show any trace of such We are, therefore, bound to accept the assumption that a purely degenerative process is present here

In general, Group III is marked by an increase of pyramidal and extrapyramidal signs, i.e., signs of central origin

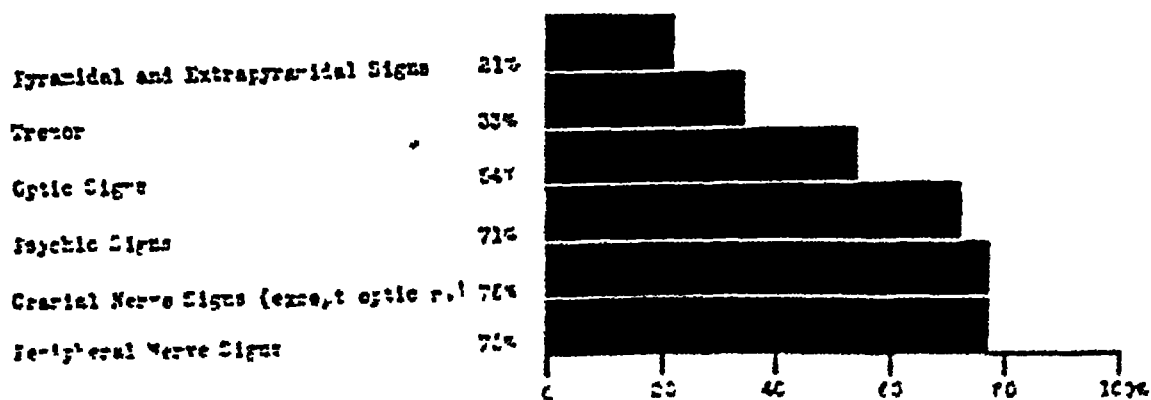
The small Group IV is composed of 10 individuals, or 8.3 per cent of those examined

NEUROLOGICAL SIGNS AND SYMPTOMS

The frequency with which pathological signs and symptoms were observed in the 120 persons included in this investigation is illustrated by the following chart (table 1).

TABLE I

Frequency of Signs of Nervous and Psychic Disturbances, Expressed in Percentages of Examination of 120 Viscose Rayon Workers



The graph demonstrates that the peripheral and cranial nerves (excluding the optic nerve), and the hemispheres (as evidenced by mental symptoms), were most commonly affected in CS₂ absorption

Disease of the nerves of the extremities is the commonest and most characteristic sign of CS₂ absorption and intoxication, 76 per cent of the 120 workers showed signs of mono- or polyneuropathy

The sensation of pins and needles, of crawling ants, a strange itching soreness (often developing from contact with rough or cold objects), and "dead" fingers (as the result of inconvenient positions of the arm) are among the earliest complaints. Arms and legs show a tendency to "fall asleep." Constant or paroxysmal pains in the muscles, especially of the calves, and in the distribution of one or several peripheral nerves are common complaints. Shooting pains in the legs often reach an intolerable intensity during the night.

Objective signs of sensory disturbance, such as tenderness of the peripheral nerves to pressure, and areas of hyperpathia have been observed in 21.7 per cent of our group, less frequently decrease of sensitivity to touch and pinprick has been noted. Ataxia and a pseudo-Romberg sign were found in 26.7 per cent.

Disease of the motor portion of the peripheral nerves, as signified by electrical over- and underexcitability, was found in 56.7 per cent. In 9.2 per cent overexcitability was seen. The mean values for the four groups are given in table 4. It may not be amiss to point out here that actual motor weakness was not found in our group of workers and that galvanic overexcitability and reaction of degeneration were seen only in a few persons. Determination of the strength-duration curve is the only way of detecting the early stages of neuropathy observed in our group.

Decrease of tendon reflexes and presence of hyperpathic areas as well as decreased sensitivity and tenderness of nerve trunks, appear to be related statistically to disease of the peripheral nerves, not of the central nervous system (table 2).

Cranial nerves Facial weakness is a rare finding in CS₂ workers. It was observed by us in only four instances. Three times it was of peripheral and once of central origin. Deviation of the tongue was slightly more frequent (10.8 per cent). Decrease of the corneal reflexes is considered one of the earliest objective signs of CS₂ absorption, whereas decrease of pupillary reflexes to light was present in about 50 per cent of our workers when examined with the Hess pupilloscope. The mean values for the four groups of severity are given in table 3. Nystagmus was one of the most frequent signs observed (77 per cent). A dip in the audiometer curve was also commonly found, workers examined showed no signs of nerve deafness but a lacuna in the hearing curve at the frequency of 4096 double vibrations (Dr O. V. Batson⁹). This hearing deficit is located above the frequencies used in speech. The isolated deficit may be caused by exposure to CS₂ or an-

other toxin affecting the cochlear nerve, such as tobacco and alcohol (Carioll and Ireland¹³), but is also present in a large number of persons for unknown reasons. The difficulties in hearing complained of by many of our workers were found not to be caused by a lesion in the hearing organ, but by the inability of the individuals to fix their attention on conversation.

The psychic symptoms which have been described in detail by F J Brace-land^{11a} are of the order of toxic psychoses. Severe insomnia and constant bad, fearful dreams are the initial symptoms, followed by rather severe memory defects and, finally, by extreme irritability and uncontrollable anger with rapid mood changes. Acute true psychoses, usually of the maniacal type, were seen in some instances though outside of the group of workers here described. Reversible interference with sexual functions in individuals below the age of 45 was reported by about 75 per cent of those examined.

The ocular signs of CS₂ absorption among viscose rayon employees have been discussed in detail by one of our coworkers, Dr Robb McDonald¹². It is sufficient to mention here that contraction of the peripheral visual fields, blurring of the optic discs, and enlargement of blind spots up to four times their normal size, have all been observed, the last in almost one-fourth of all those examined. Two persons gave a history suggestive of having had a central scotoma at some previous time, and one was found to have poor central color vision. Arteriolar-sclerosis was found in a number of individuals far below the usual age for its occurrence. However, the majority of ocular complaints were due to lack of proper glasses.

Some signs of involvement of the pyramidal or extrapyramidal system were present in 27.5 per cent of our material, 21.7 per cent, or about every sixth man, showed the more or less characteristic picture of Parkinsonism. Quarelli,¹⁴ in Italy, who first described this syndrome in CS₂ intoxication, saw it in 30 per cent of the viscose rayon workers of Torino. Many of his patients, according to a report of Audo-Gianotti,¹⁵ showed tremor as the only sign of Parkinsonism; but in many cases the tremor was a static one, disappearing in repose and increasing on voluntary movements. In other words, not every tremor in CS₂ absorption is a Parkinson tremor. We based our diagnosis essentially on the appearance of the individual, his behavior, rigidity, the absence of arm-swinging in walking, positional and postural reflexes, and the Noica test. Parkinsonism in CS₂ may or may not be combined with polyneuropathy. In some instances signs indicating a lesion of the basal ganglia were found combined with those pointing to involvement of the optic thalamus. We saw three persons with a typical thalamic syndrome.

Poor exercise tolerance, palpitation, shortness of breath, precordial and substernal pain were common complaints in this group of workers and were suggestive of some cardiac derangement (Dr S. Bellet). Objective signs of cardiovascular disease were seen in about one-third of all examined, though they were of minor nature in some instances. Bradycardia ranging from 50 to 60 pulse beats per minute was frequently observed. Electro-

cardiographic changes were found in every eighth of our viscose rayon workers. They consisted of slurring of the ventricular complex, depression of the S-T interval and inversion of the T-wave. Arteriosclerosis of peripheral and retinal blood vessels with or without associated arterial hypertension or angina pectoris in young persons was more frequently observed in this group than in the average of the entire population. Our human material is not great enough to indicate in itself a definite causal relationship between the cardiovascular changes and the CS₂ absorption. It may be of significance in this connection that dogs during experimental chronic CS₂ intoxication developed retinal spasms and a negative T-wave in the electrocardiogram and showed marked arteriofibrosis of the cortical blood vessels.²³

Biochemical Examinations The spinal fluid has been examined in a number of persons with CS₂ intoxication, not included in this study, and has always been found normal.

Determination of CS₂ in blood and urine of viscose rayon workers has been made in two factories by J. H. Frank, with his xanthogenate method, about 30 to 60 minutes after the workers had left the plant. In the one plant, of a group of 19 workers only one (5 per cent) did not show CS₂ in his blood; the others, churn room and spinning room workers, had a mean of 409 ± 248 γ CS₂ with a range from 129 to 1219 γ . The urine values of CS₂ in this group were 27 ± 6.3 γ , with a range between 20 and 50 γ . In the other factory, of a group of nine spinning room workers, two were negative in the blood test, one showed traces and six a mean of 15 ± 7.5 γ one hour after leaving the plant. The urine in the same group at the same time was negative in five, showed traces in three, and 6 γ in one man. Our systematic experimental investigations, in addition to the clinical data, suggest that CS₂ is eliminated from the body within about four hours from the blood and probably within a day from the urine. This fact limits the possibility of proving the nature of intoxication.

The porphyrine excretion in the 24 hour urine specimens of eight workers exceeded the normal figures (0.03 to 0.05 mg) in only one instance (0.07 mg) (Dr. J. H. Austin).

Serum cholesterol In a random sample of 100 normal individuals the mean of the total serum cholesterol was 178.28 mg per cent with a standard error of 1.3 and a standard deviation of 13.11 mg per cent, of which about 60 per cent were esters. The mean of the total cholesterol values was 34 per cent higher in the 54 CS₂ workers than in the normal workers, simultaneously with a fall of the percentage of the cholesterol esters (238 mg per cent total cholesterol with a standard error of 6.1 and a standard deviation of 44 mg per cent, of which 44 mg per cent were esters (Dr. J. G. Reinhold)). The high serum cholesterol value was found not to be associated statistically with retinal or peripheral arteriosclerosis, but seems to represent an independent disturbance of metabolism, possibly a toxic disorder of the liver function.

* The second figure means in this paragraph standard deviation.

Hematological studies (Dr A J Creskoff) revealed rather normal conditions except for a slight increase in the monocyte percentage. The monocytes also showed certain indications of toxicity (basophilia, toxic granulations).

Pointing to dysfunction of the liver is furthermore the fact that in 20.8 per cent of all persons examined, varying degrees of sore, red, smooth, or atrophic tongues were recorded, while 8.3 per cent suffered from ecchymoses and frequently bleeding gums and noses. These observations, together with polyneuropathy, are suggestive of a vitamin B deficiency.

The average thiamine excretion in 24 hour specimens of urine from five normal individuals was found to be 516 γ with a standard error of 25.8 and a standard deviation of 141 γ in 30 determinations performed by Jolliffe, Goodhart, Gennis and Cline¹⁶. Dr Leon Jonas examined the 24 hour specimens of eight spinning room workers*. One of them had a normal excretion of 405 γ ; the other seven had values ranging from 54 to 197 γ .

It may be mentioned in passing that the person with the lowest thiamine output (54 γ) had the highest CS₂ content in his blood and urine (1 mg and 50 γ respectively), and had, in addition, a cholesterol level of 328 mg per cent. He was a member of Group IV, which contained the most severely affected persons.

Considering the rôle of the liver in vitamin B deficiency,¹⁷ the increase of total cholesterol and the decrease of its esters in our workers (a phenomenon usually observed in severe liver damage), one might wonder whether CS₂, like carbon tetrachloride, does not act primarily upon the liver, depleting it of its vitamin stock and leading in this way secondarily to polyneuropathy. If this were so, a high-fat diet should have the same detrimental effect on the course of experimental CS₂ intoxication that it has in carbon tetrachloride poisoning. Our experiments on dogs suggest that this is the case.

CONCLUSIONS

There is no one symptom or sign characteristic of CS₂ absorption or intoxication, but the syndrome as a whole is fairly typical. Psychic symptoms such as sleeplessness and bad dreams followed by fatigue, listlessness and loss of initiative are usually the first and most consistent warning signs. They are accompanied very soon by disturbance of electrical excitability in some extremity muscles, and by decrease of the pupillary and corneal reflexes. Tenderness of nerve trunks to pressure, hyperpathic skin areas, paresthesias, and pain are common in CS₂ absorption, as are nystagmus and an isolated hearing loss at 4096 frequencies. Retrobulbar neuropathy, pyramidal signs and Parkinsonism may be present. The total serum cholesterol is often markedly increased, and the percentage of the esters simultaneously decreased. The thiamine excretion shows a tendency to low values. The spinal fluid is normal.

The presence of this syndrome should always arouse the suspicion of exposure to CS_2 , but unless exposure can be established by factual testimony no direct proof can be evidenced by medical or chemical tests, since CS_2 disappears from blood and urine within a short time after the end of exposure.

STATISTICAL DATA AND THEIR EVALUATION

The majority of signs of disease here mentioned were discovered years ago without the aid of modern apparatus. There is no doubt that a piece of cotton wool and a pin are all that are necessary to detect motor weakness, sensory loss, decrease of corneal and pupillary reflexes, provided that the disturbance is massive enough to be seen with the naked eye. However, CS_2 intoxication is a good example of the experience that reliance on the "established" qualitative methods has led to erroneous statements such as that of the frequent occurrence of poor vision and hearing and, on the other hand, the overlooking of early stages of peripheral neuropathy and of the beginning decrease of corneal and pupillary reflexes. We like to stress the point that to our knowledge there is no way of early detection of this and many other neural diseases except by the application of the most sensitive apparatus giving numerical and reproducible results. The time has passed when the physician could complacently wait until his patients' symptoms and signs had reached the point where diagnosis could not possibly be missed. The recovery period from CS_2 poisoning is closely related to the hours of exposure. No instrument should be considered too complicated if with its help the time of absenteeism could be shortened. We have learned, finally, that in dealing with a great number of persons suffering from the same disease, and in integrating and combining their symptoms and signs, figures cannot always be taken at their face value but have to be examined for their significance. It should be understood that statistics is not a method of twisting the facts but of testing the validity of their interpretation.

We have mentioned that certain combinations of clinical signs and symptoms were found more frequently than others. It remains to demonstrate how far such an association could be considered as significant, i.e., probably not due to chance. Application of the chi square test shows a significant association only between the signs listed in table 2, A 1-5. The first computation indicates that CS_2 acts on the optic nerve, despite its central nature, in the same way as it does on peripheral nerves, the second shows that the vascular changes in the retina are probably not the result of a local process but part of a systemic vascular disease which finds its expression in arterial hypertension and electrocardiographic changes in younger people. Furthermore, decrease of pupillary and corneal reflexes is closely associated while their occurrence is not related to any other neural sign including abnormal electrical irritability of the peripheral nerves. In other words, there is no statistical evidence that the lesion responsible for the decrease of these two reflexes is situated in their afferent or efferent cranial nerves.

Finally, it is interesting to see that the occurrence of pyramidal and extra-pyramidal signs is statistically not associated with disease of the peripheral nerves, i e , is possibly due to a different mechanism

It has been mentioned above that all cases were graded arbitrarily according to their severity by consensus of the six cooperating specialists What significance can be attributed to this vote?

TABLE II
Significant Association between (A) Pathological Signs and between (B) Severity of Disease and Pathological Signs

A	1 Retrobulbar neuritis vs peripheral neuropathy (incl electr irritability, contraction of visual fields, enlargement of blind spots),	P* = < 0 001
	2 Retinal vascular disease vs peripheral vascular disease,	P = 0 05
	3 Decreased pupillary vs corneal reflexes,	P = 0 05
	4 Pyramidal vs extrapyramidal signs,	P = 0 0001
	5 Decreased electrical irritability vs decreased tendon reflexes and sensitivity as well as presence of hyperpathic areas	P = 0 01
B	1 Severity of disease vs disturbances of peripheral nerves (decrease of sensitivity, tenderness of nerve trunks, areas of hyperpathia),	P = 0 01
	2 Severity of disease vs electrical irritability of nerve-muscle apparatus,	P = 0 034
	3 Severity of disease vs psychic symptoms.	P = 0 05

* P indicates the probability that an association of the given amount or greater would occur in any random sample of a certain size taken from a universe in which there was no association between the given factors For example If there were no relationship between the occurrence of mental symptoms and the severity of carbon disulphide poisoning in all people who might have been subjected to our tests, it would have been unlikely (less than five chances in 100) that we would find the connection established between these two factors in our sample A probability of 0 05, i e , of one in 20, or less, is taken to be significant by Fisher and most other statisticians (see R A Fisher, Statistical Methods for Research Workers)

Table 2, B 1-3, indicates that a significant association between the estimated severity of disease and the various pathological signs exists only in reference to disturbances of the peripheral nerves, abnormal electrical irritability of the nerve-muscle apparatus and psychic signs In other words, retrospective evaluation suggests that peripheral neuropathy and mental behavior were the most important of the factors studied in grading the severity of our 120 cases and should be considered as such in the future

Tabulation of the frequency of clinical signs—such as ataxia, Romberg, pyramidal and extrapyramidal signs, decrease of pupillary and corneal reflexes and the electrical irritability of the finger extensors and flexors and peroneal muscles—in the various groups of severity shows an interesting phenomenon The first four of the above mentioned signs were found in 6 4 per cent to 21 3 per cent of the 47 persons considered as mildly affected by CS₂ Tenderness of the nerve trunks to pressure and tremor were the most frequent signs in this group The frequency with which these signs were encountered increased—as could be expected—in the groups of more severely affected workers

However, pupillary and corneal reflexes as well as electrical irritability of the nerve-muscle apparatus behaved differently. A pathological reaction of the pupils to light was present in 30 2 per cent of 34 mildly affected indi-

viduals. This frequency did not vary by more than 5 per cent in the groups containing cases of greater severity. To give another example, decreased electrical irritability of the finger extensors was found in 62 per cent of 47 workers in the mildest group, decreasing to 50 per cent in the next two groups and reaching 66.6 per cent in the 10 persons most severely affected.

In other words, the number of persons showing one of the first four signs increased with the higher degree of severity of CS₂ absorption, while the number of persons showing abnormal pupillary and corneal reflexes or electrical irritability remained almost the same from the group of the mildest to that of the severest cases.

TABLE III

Mean (M) and Standard Error (SE) of Percentage of Difference of Illumination Required to Elicit Pupillary Reactions and of the Strength of a Jet of Air Required to Elicit Corneal Reflexes in Normal Individuals and in CS₂ Workers Grouped According to Various Degrees of Severity (S)

N = Number of Observations				r = Correlation Coefficient		P = Probability	
S	Pupillary Reflex			N		Corneal Reflex	
	N	M	SE			M	SE
Normal	138	4.6 ± 0.07%		148		0.42 ± 0.02 mg/mm ²	
I	34	7.7 ± 0.41%		76		0.49 ± 0.04 mg/mm ²	
II	31	8.9 ± 0.64%		39		0.63 ± 0.07 mg/mm ²	
III	19	9.8 ± 1.32%		26		0.78 ± 0.08 mg/mm ²	
IV	8			6		1.05	
r = +0.96				+0.97			
P = 0.04				0.007			

Decrease of pupillary and corneal reflexes and of electrical irritability of the nerve-muscle apparatus has been determined in figures permitting computation of their mean and standard error in each of the four groups of severity. Table 3 shows clearly the rectilinear, significant progress of the decrease of function from normal over groups I to IV.

The same holds true for the increase of electrical underexcitability of the finger extensors from normal values over groups I to IV which is significant.

TABLE IV

Mean (M) and Standard Error (SE) of Electrical Underexcitability of Three Muscle Groups in Normal Persons and in CS₂ Workers Grouped According to Various Degrees of Severity (S)

N = Number of Observations r = Correlation Coefficient P = Probability

S	Finger					Peroneal Muscles	
	Extensor	M	SE	Flexor		M	SE
	N			M	SE		
Normal	40	7.7 ± 0.12√μC		4.8 ± 0.13√μC		4.5 ± 0.11√μC	
I	47	11.8 ± 0.38√μC		9.0 ± 0.33√μC		6.6 ± 0.24√μC	
II	34	13.5 ± 0.65√μC		9.3 ± 0.23√μC		10.7 ± 1.06√μC	
III	25	15.8 ± 1.18√μC		(6.5)		7.3 ± 0.27√μC	
IV	9	18.9 ± 0.77√μC				9.9 ± 0.9√μC	
r = +0.99				+0.89		+0.81	
P = 0.001				>0.1		>0.1	

whether we compute the difference of the means from group to group or the correlation coefficient over the whole range (table 4). A similar increase of electrical excitability can be demonstrated for the finger flexors and the peroneal muscles, but this increase is not significant

These computations strengthen the clinical impression, namely, that examination of the pupillary reaction to light with the aid of the Hess pupillo-scope, of the corneal reflexes* with the help of graded jets of air, and of the electrical excitability of the common finger extensor by determining its strength-duration curve, are the most accurate and rapid methods of estimating the degree of CS₂ absorption and the damage done to the nervous system, if CS₂ is known to be the noxious agent. The first two methods are, in addition, so simple that they may be applied by a technician in industrial routine examinations

DISCUSSION

CS₂ is one of the best fat solvents. The conclusion was obvious, therefore, that it dissolves in the myelin sheaths of the nerve fibers just as it was assumed that alcohol acts in this way upon the nervous system (Mattei and Sédan¹⁸). As far back as 1877 Binz¹⁹ had compared the effect of CS₂ upon the nervous system to that of alcohol and also of chloral and chloroform. This relationship had already been suggested by Simpson²⁰ when he used CS₂ in 1848 as a gaseous anesthetic for amputation of the breast before he finally recommended chloroform as the best narcotizing agent. This behavior, which was later confirmed by Lehmann,²¹ permits little doubt that CS₂ acts as a narcotic upon the surface membranes of the brain cells.

However, this is only one side of the problem. Carbon disulphide, in contrast to chloral and chloroform, has a noxious effect upon the peripheral nerves, the first signs of which may appear as late as four days after the actual intoxication has ceased (MacGregor²²). In our animal experiments these signs were observed in the fourth week after the onset of the intoxication (Lewey et al²³). This delay in the development of the peripheral neuropathy, in contrast to the immediate effect of CS₂ on the hemispheres, raised the question as to whether another link might be intercalated between the CS₂ absorption and the lesions in the spinal cord, brain stem, or peripheral nerves. This hypothesis is strengthened by the fact that no statistical association has been found between the appearance of the psychic symptoms and brain stem or peripheral nerve signs. A further suggestion of a difference in the mechanism of action in acute and chronic CS₂ absorption might be seen in the observation that the number of persons with mental symptoms increased gradually from the group of the slightest to that of the severest cases; whereas the number of persons with involvement of the peripheral nerves was almost the same in all four groups but showed an increase in the severity of the neuropathy. All these considerations suggest that the mecha-

* Corneal scars due to H-S in spinner room workers should be taken into consideration.

nism through which CS_2 acts on the hemispheres is different from that effective in the rest of the nervous system

Such a dualistic action in the acute and chronic effects of alcohol is believed to be an established fact today. If the dualistic action recognized in alcohol may be justifiably extended to CS_2 its effect should not be regarded any more as a direct lipolytic effect on the myelin but, similar to that of alcohol, as a neuropathy in consequence of thiamine deficiency

In fact, histopathological examination of the peripheral nerves in CS_2 intoxication shows that the axis cylinders of the peripheral nerves disintegrate first while the myelin sheath is still in a fairly good condition (Alpers and Lewey^{11b})

Evidence has been given that in CS_2 absorption the thiamine excretion in the urine is markedly decreased and that treatment with thiamine rapidly improves the peripheral neuropathy. Finally, our animal experiments with CS_2 show that daily injections with thiamine delay the development and the death of the animals

We may go one step further. We have previously stated our reasons for assuming that involvement of the liver and depletion of its stock of vitamin B appear to be one of the essential factors in the occurrence of neuropathy.¹⁷ Furthermore, we have known for a long time that carbon tetrachloride, another excellent fat solvent, produces severe liver damage, and that the onset of the pathological signs in this intoxication is accelerated by a diet rich in fat. Carbon disulphide shows in our animal experiments a similar relationship. These experiments suggest, in addition, that poisoning of coenzymes active in nerve metabolism may be another important factor in the occurrence of neuropathy in CS_2 intoxication

If these considerations are confirmed it appears that an adequate diet, especially in the cafeterias of plants using CS_2 , may prove helpful in the task of preventing CS_2 intoxication. It is only proper to give credit to Delpech²⁴ who, in 1856, recommended a regimen rich in lean meat—a very unusual diet in France—as the most effective precautionary measure for workers in rubber plants

SUMMARY

1 This is a report of the neurological and medical findings in 120 viscose rayon workers exposed to various degrees of chronic carbon disulphide (CS_2) absorption. With three exceptions, all these men were at work

2 Chronic CS_2 absorption may involve all parts of the central and peripheral nervous system. CS_2 absorption is initiated by psychic symptoms later accompanied by peripheral neuropathy and diseases of the cranial nerves, decrease of corneal and pupillary reflexes, as well as by pyramidal and extrapyramidal signs. Varying degrees of Parkinsonism have been observed and, in three persons, a true thalamic syndrome

3 Subjective and objective symptoms and signs of cardiovascular disease were found in one-fourth of the subjects examined. Arterial hypertension was observed in an unusually great number of young individuals. The mean of the total serum cholesterol values was found 34 per cent above normal with a simultaneous decrease of the values of the cholesterol esters.

4 Graphs illustrate the frequency of signs and symptoms. Some of the pathological signs become more frequent from group to group; others do not, but become severer instead.

5 The hypothesis is proffered that the mechanism of chronic CS_2 absorption is different from that of acute CS_2 intoxication. The first is attributed to thiamine deficiency, possibly by way of a liver damage and by direct poisoning of the coenzymes of nerve metabolism and respiration whereas the second is compared with the narcotic effect of other gaseous anesthetics.

6 The importance of a diet rich in vitamin B in the cafeterias of plants using CS_2 is suggested.

I wish to express my appreciation to the Department of Labor and Industry of the Commonwealth of Pennsylvania and my gratitude to all who have cooperated in this survey.

BIBLIOGRAPHY

- 1 BARD, C. L. Insanity due to CS_2 , *South California Pract*, 1892, vii, 481.
- 2 PETERSON, F. Three cases of acute mania from inhaling CS_2 , *Boston Med and Surg J*, 1892, cxxvii, 325.
- 3 HEATH, F. C. Amblyopia from CS_2 poisoning, *Arch Ophth*, 1902, vi, 4.
- 4 JUMP, H. D., and CRUICE, J. M. Chronic poisoning from CS_2 , *Univ of Pennsylvania Med Bull*, 1904, xvii, 193.
- 5 FRANCINE, A. P. Acute CS_2 poisoning, *Am Med*, 1905, ix, 871.
- 6 GORDY, S. T., and TRUMPFER, M. CS_2 poisoning with a report of six cases, *Jr Am Med Assoc*, 1938, cx, 1543.
- 7 HAMILTON, A. Industrial poisons in the United States, 1925, Macmillan, New York, p 366.
- 8 HAMILTON, A. The making of artificial silk in the United States and some of the dangers attending it, *Div of Labor Standards, U S Dept of Labor*, 1937, Bull No 10, 151.
- 9 Survey of CS_2 and H_2S hazards in the viscose rayon industry, *Occupational Dis Prevention Div, Dept of Labor and Industry of Pennsylvania*, 1938, Bull No 46.
- 10 HAMILTON, A., and LEWEY, F. H. CS_2 and H_2S hazards in the viscose rayon industry, *Trans VIII Internat. Congr f Industr Surg and Occupational Dis, Frankfurt a M*, p 1107, 1938.
- 11a BRACFLAND, F. J. Mental symptoms following carbon disulphide absorption and intoxication. In print.
- 11b ALPERS, B. J., and LEWEY, F. H. Changes in the nervous system following CS_2 poisoning in animals and man, *Arch Neur and Psychiat*, 1940, xiv, 725.
- 12 McDONALD, R. CS_2 poisoning, *Arch Ophth*, 1939, xx, 839.
- 13 CAPROTT, F. D., and IRELAND, P. F. Association of toxic deafness with toxic amblyopia etc. *Arch Otolaryng*, 1935, xvi, 459.
- 14 QUARANTE, G. L'intossicazione professionale da CS_2 . *Trans V Internat Congr Occupational Dis, Budapest*, 1928.
- 15 ALBERGIANOTTI, G. B.: Le Parkinsonisme sub' carbonio protozoico. *Presse med*, 1932, vi, 1289.

- 16 JOLLIFF, N, GOODHART, R, GUNNIS, J, and CLINE, J K The experimental production of vitamin B₁ deficiency, etc, Am Jr Med Sci, 1939, cxviii, 198
- 17 LEWIS, F H Vitamin B deficiency and nervous disease, Jr Nerv and Ment Dis, 1939, lxxix, 1 and 174
- 18 MATTEI, C, and SLDAN, I Contribution a l'étude de l'intoxication par le CS₂, Ann d Hyg, 1924, ii, 385
- 19 BIRZ, C Z Wirkungsweise schlafmachender Stoffe, Arch f exper Path, 1877, vi, 310
- 20 SIMPSON, J Y Notes on the anesthetic effects of chloride of hydrocarbon, nitrate of ethyl, benzene, aldehyde and bisulphurate of carbon, Monthly Jr Med Sci, 1848, viii, 740
- 21 LEHMANN, K B Studien ueber die Absorption einiger giftiger Gase u, Daempfe a d Organismus, Arch f Hyg, 1892, vii, 324
- 22 MACGREGOR, R D Supposed poisoning by the daily use of carbon disulphide, Med Jr Australia, 1892, xi, 622
- 23 LEWIS, F. H, and coworkers Experimental chronic carbon disulphide poisoning in dogs, Jr Indust Hyg, 1941, xxiii (Nov)
- 24 DELPECH, A. Accidents que développe, chez les ouvriers en caoutchouc, l'inhalation du CS₂ en vapeur, Union med, 1856, x, 265 Industrie du caoutchouc soufflée Recherches sur l'intoxication speciale que détermine CS₂, Ann d Hyg, 2e ser, 1863, xix, 65

THE SOLUBILITY OF ACETYLSULFAPYRIDINE AND ACETYLSULFATHIAZOLE IN THE URINE *

By ARTHUR C CURTIS, M D , F A C P . and SIDNEY S SOBIN, P H D ,
Ann Arbor, Michigan

SHORTLY after the introduction of sulfapyridine into clinical medicine, hematuria was described as one of the common and dangerous complications of this type of therapy. Acetylsulfapyridine was demonstrated as the excretory form of the drug,^{1, 2, 3} and the relationship between crystals of acetylsulfapyridine in the urine and hematuria was quickly recognized^{4, 5, 6, 7, 8}

This work was begun to record the solubility characteristics of acetylsulfapyridine and to determine the type and the amount of urine necessary to effect complete solution of this material. Our method was as follows. A portion of urine was concentrated to a specific gravity of 1.030. Aliquots were taken and adjusted to varying pH between 5.5 and 8.0 by electrometric titration. These samples were further treated with distilled water so that for each different pH range a set of specific gravities from 1.005 to 1.030 was set up. A small amount of each of these solutions, to which had been added an excess of powdered acetylsulfapyridine, was incubated at body temperature for one hour, occasionally shaken and then filtered. The concentration of sulfapyridine in each solution was then determined by the method of Bratton and Marshall after acid hydrolysis (using N-(1-naphthyl)ethylenediamine dihydrochloride in the coupling reaction).⁹

The results of our determinations of the concentration of acetylsulfapyridine in urines of different pH and specific gravities is seen in chart 1. Each graph represents a determination at the specific gravity indicated: 1.005, 1.010, 1.015, 1.020, 1.025, and 1.030. The concentration of acetylsulfapyridine in milligrams per cent is plotted on the ordinates and the pH on the abscissae. It appears from chart 1 that a change in solubility of the drug occurs with the changing pH. There is some tendency for this to represent a straight line function, but it is quite apparent that the concentration varies little on the acid side of neutrality. As soon as the pH of 7.0 is reached, the solubility curve rises sharply. In actual values, the concentration of acetylsulfapyridine below a pH of 7.0 is between 20 and 30 milligrams per cent and above a pH of 7.0 between 30 and 40 milligrams per cent.

Although it is not possible to predict the solubility characteristics of chemical substances, it was quite unexpected to find the solubility of the acetylsulfapyridine to increase as the specific gravity of the urinary solutions

* Received for publication: February 15, 1941.
From the Department of Internal Medicine, University of Michigan Medical School
Ann Arbor

increased This is illustrated in chart 1 If the solubility curves plotted are superimposed upon a single graph, there is obtained a series of almost parallel lines, one staggered above the other, with the solubility curve at a

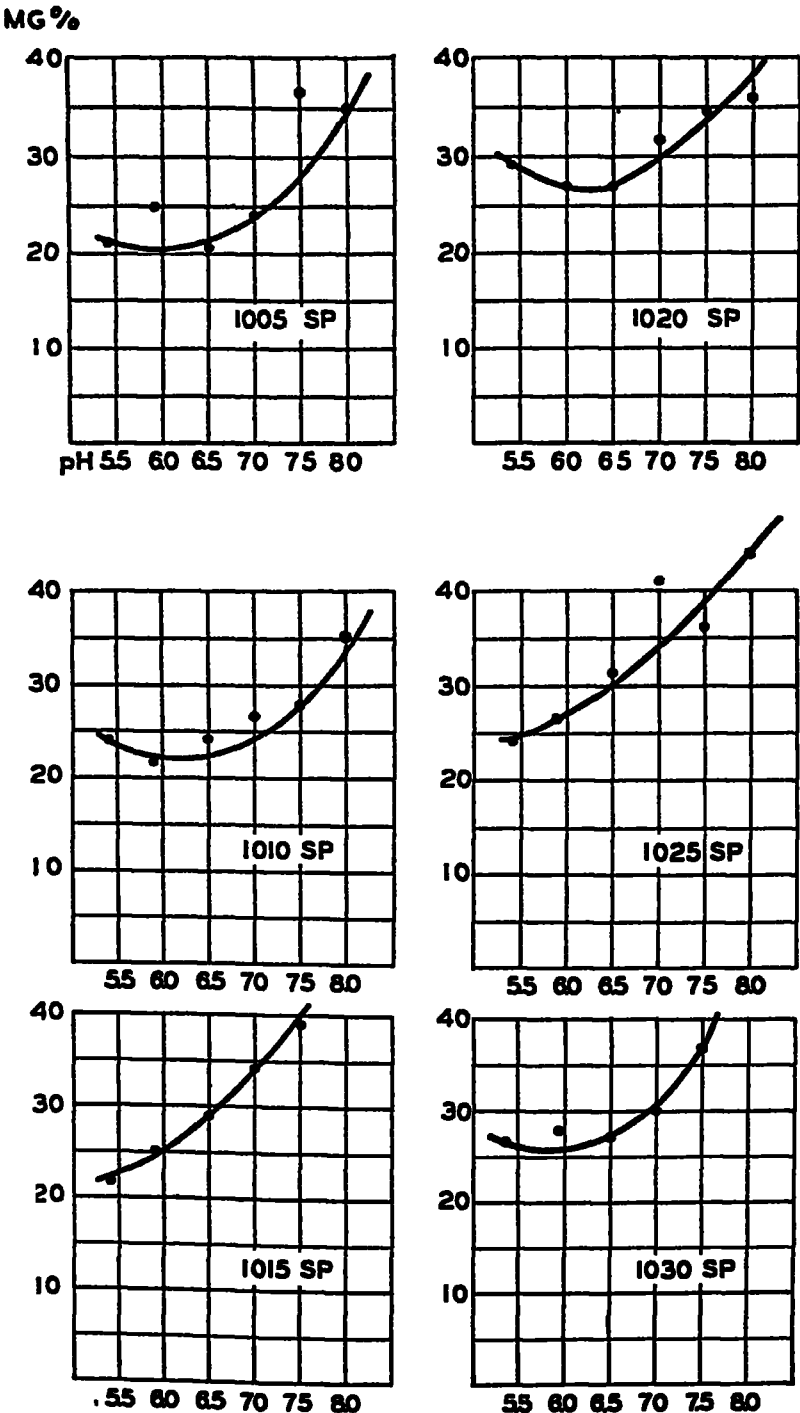


CHART 1 The effect of pH and specific gravity on the solubility of acetylsulfapyridine in urine

Each graph represents the solubility in milligrams per cent of acetylsulfapyridine at the specific gravity indicated SP = Specific Gravity

specific gravity of 1.005 below, and a curve falling between the solubility curves 1.025 and 1.030 above.

Of the several urinary constituents, urea was suspected of playing some rôle in the phenomenon observed. We accordingly repeated our earlier observations, using a urine of low specific gravity (1.005) and sufficient amounts of concentrated urea solution to increase the specific gravity to the levels 1.010, 1.015, 1.020, 1.025, 1.030. Chart 2 shows the results of this

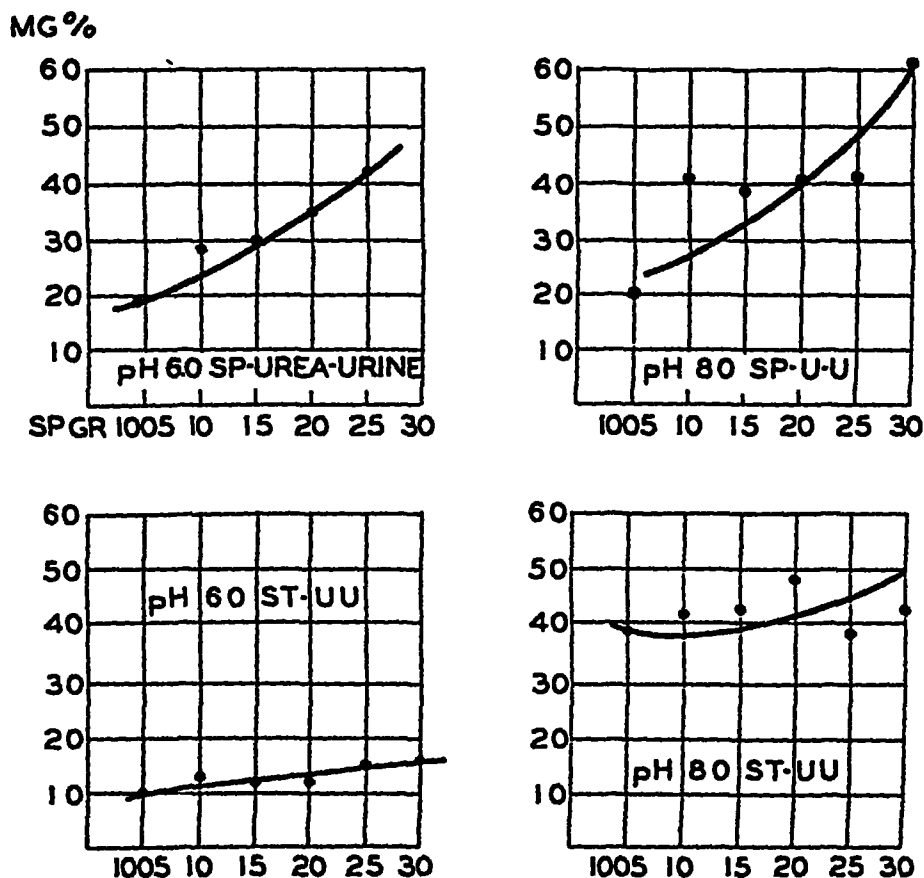


CHART 2 The effect of pH and increasing concentration of urea on the solubility of acetylsulfapyridine and acetylsulfathiazole

SP = Acetylsulfapyridine
ST = Acetylsulfathiazole
U-U = Urea-Urine Solution

series of determinations. Concentration in milligrams per cent is plotted on the ordinates and specific gravity on the abscissae. The figures above are those of acetylsulfapyridine and below those of acetylsulfathiazole. Those on the left are for a pH of 6.0, and on the right for a pH of 8.0. It is again evident that the solubility of acetylsulfapyridine increases with the specific gravity and with alkalinity. In this particular group of experimental data, solubility is proportional to increasing amounts of urea. The solubility of acetylsulfathiazole is much more marked in alkaline than in acid solutions as compared with acetylsulfapyridine, but increasing amounts of urea seem to affect its solubility little. Other non-reported data confirm this finding.

To determine finally just what effect an increase in specific gravity itself would have, exclusive of any urea effect, we repeated these observations with aqueous solutions of urea and dextrose to which was added acetylsulfapyridine. The results are shown in chart 3. The marked solvent effect of increasing amounts of urea is apparent. On the other hand, the solutions with dextrose show relatively no change in solubility with increasing amounts of solute. Urinary solutions show this effect in a more striking manner.

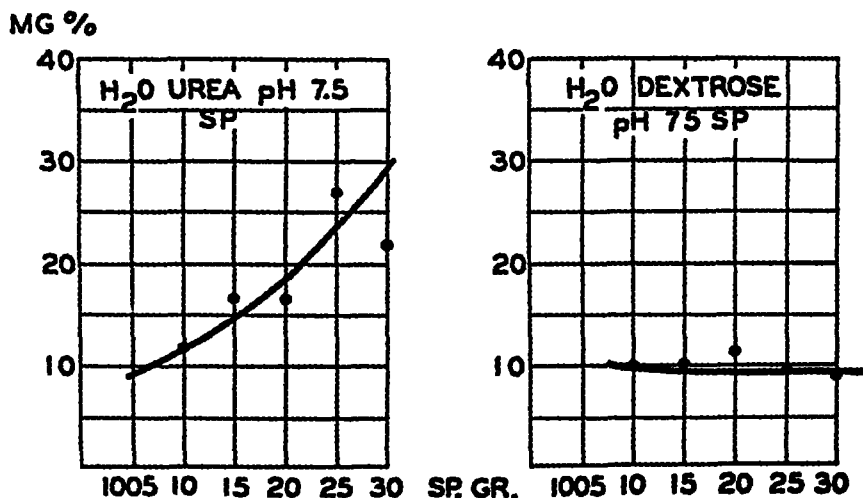


CHART 3 The effect of increasing concentration on urea and of dextrose on the solubility of acetylsulfapyridine in aqueous solution

Volume ratios for urines of specific gravities 1.005 and 1.030 are 2.5 : 1. The clinical advantage of either specific gravity depends upon the relative solubility of acetylsulfapyridine at that specific gravity. Although the solubility of acetylsulfapyridine at a specific gravity 1.030 may be appreciably greater than its solubility at a specific gravity 1.005, it is not two and a half times the solubility in the latter solution. Accordingly, from our studies, the greater volume of the more dilute urine is more desirable.

Common dosages of sulfapyridine lie between 2 and 6 grams a day. An average figure for the absorption of sulfapyridine is about 50 or more per cent^{8, 10, 11}. The urinary excretion of either the free or combined form is almost quantitative for the amounts absorbed⁸. It has been further shown that the urinary excretion of the conjugated drug is about 50 or more per cent^{8, 11}. This means that at least one-quarter of the oral daily dose is excreted in the urine as acetylsulfapyridine. If the daily oral dose of sulfapyridine is two grams, about 500 milligrams would be excreted as the acetylated form in the urine. If the daily oral dose of sulfapyridine is six grams, 1,500 milligrams would be excreted as the acetylated form in the urine. In an acid urine of low specific gravity acetylsulfapyridine is soluble to about 25 milligrams per cent. To prevent acetylsulfapyridine crystals from forming in this type of urine a urinary output of 2,000 c.c. would be necessary.

for a two gram daily intake, and 6,000 c c for a six gram daily intake. On the other hand, with an alkaline urine, the solubility is about 40 milligrams per cent and the urine output necessary for solution of the acetyl form of the drug would be decreased to 1,250 c c. for a two gram daily dose, and 3,750 c c for a six gram daily dose (chart 4)

Dose	Absorption Excretion	Excretion Acetylated (50%)	pH <7.0 Urine Volume 25 mg % Soln	pH >7.0 Urine Volume 40 mg % Soln
2 gm	1 g.	500 mg	2000 c c	1250 c c
6 gm	3 g	1500 mg	6000 c c	3750 c c

CHART 4 Urine volume necessary to effect complete solution of acetylsulfapyridine with pH less and greater than 7.0

The solubility of acetylsulfathiazole shows a much more marked response to acidity and alkalinity changes than does acetylsulfapyridine. In a urine of specific gravity 1.005 at a pH 5.5-6.0, this material is soluble in amounts less than 10 milligrams per cent. If this is compared to the solubility of acetylsulfathiazole in a similar urine at a pH of 8.0-8.5, where the solubility is between 30-40 milligrams per cent, a 300 to 400 per cent increase in solubility is present.

We do not wish to discuss the problem of how hematuria is produced by the sulfonamide compounds, but we have assumed, from the many reports, that when it does occur, it is a result of trauma to the genito-urinary tract by the acetylated form of the drugs that produce it.

There is increasing evidence that some conjugation other than the acetyl form occurs.² Glycuronate¹² excretion is so far indicated. Just what proportion of total excreted drug may occur in these forms has not been determined.

SUMMARY

1. To prevent the precipitation of acetylsulfapyridine and acetylsulfathiazole crystals in the urine, the fluid output must be sufficient to hold all of these compounds in solution.

2. The solubility of both acetylsulfapyridine and acetylsulfathiazole is greater in an alkaline urine than in an acid urine, so that enough base should always be taken with these drugs to keep the pH of the urine alkaline.

3. Urea seems to have some importance in the solubility of acetylsulfapyridine in the urine.

BIBLIOGRAPHY

1. MARSHALL, E. K. JR., BOSTON, A. C., and LITCHFIELD, J. T. The toxicity and absorption of 2-sulfanilamido-pyridine and its soluble sodium salt, *Science*, 1939, lxxviii, 595.
2. RATH, H. D., BUDOVY, J. G. M., AVIS, J. B., and SCOTT, J. F. Urinary excretion product of sulfapyridine, *J. Biol. Chem.* 1939, cxxviii, 279.

- 3 BAILEY, E J, and WILKINSON, R The absorption and excretion of 2-sulfamyl-aminopyridine, Quart. Jr and Year Book of Pharmacy, 1939, **xxii**, 4
- 4 SOUTHWORTH, H, and COOK, C Hematuria, abdominal pain, and nitrogen retention associated with sulfapyridine, Jr Am Med Assoc, 1939, **cxii**, 1820
- 5 LAWRENCE, E A Recent advances in the treatment of pneumonia, Internat Rev Recent Adv in Med, 1939, **iii**, 48
- 6 SNAPPER, I, LIU, S H, CHUNG, H L, YU, T F, and SUN, H M Hematuria, renal colic and acetylsulfapyridine stone formation, Chinese Med Jr, 1939, **lvi**, 1
- 7 GRAHAM, D, WARNER, W P, DAUPHINEE, J A, and DICKSON, R C The treatment of pneumococcal pneumonia with daganan, Canad Med Assoc Jr, 1939, **xl**, 325
- 8 LONG, P H, and WOOD, W B, JR Observations upon the experimental and clinical use of sulfapyridine II The treatment of pneumococcal pneumonia with sulfapyridine, ANN INT MED, 1939, **xiii**, 487
- 9 BRATTON, A C, and MARSHALL, E K, JR New coupling component for sulfanilamide determination, Jr Biol Chem, 1939, **cxviii**, 537
- 10 SCHMIDT, L H, and HUGHES, H B Absorption and excretion of sulfanilamidopyridine, Proc Soc Exper Biol and Med, 1939, **xl**, 409
- 11 STOKINGER, J E Absorption, acetylation, and excretion of 2-sulfanilamidopyridine, Proc Soc Exper Biol and Med, 1930, **xl**, 61
- 12 SCUDI, J F, RATISH, H D, and BULLOWA, J G M Increased glycuronate excretion following administration of sulfapyridine, Science, 1939, **lxxix**, 516

ARSENICAL SENSITIVITY AND VITAMIN C

By MAHLON H. DELP, M.D., and C. J. WEBER, M.D.,
Kansas City, Kansas

WITH the advent of arsenic as a spirochetocide, the physician found that one of his great problems in handling the syphilitic patient was that of avoiding, if possible, the toxic manifestations of this therapeutic agent, or of treating them if they appeared. Numerous improvements in arsenical preparations and improvements in the technic of their administration have not yet eliminated these problems. Toxic manifestations take many forms—from the milder gastrointestinal disturbances to the severe hemorrhagic encephalitis—with the intermediate complications of hepatitis, purpura, and arsenical dermatitis occurring all too frequently. In a large antisyphilitic clinic, constant and individual attention must be given to the patient receiving therapy in order to complete his treatment without producing a complication more serious than the original disease. All attempts at finding any agent capable of successfully neutralizing this toxicity of arsenic have failed. Likewise, all agents used in treatment of the complications have been found wanting in efficacy.

Recently there have been several reports in the literature on the relationship of vitamin C and neoarsphenamine sensitivity, both experimental and clinical in character. Chapman and Morrell¹ reported a group of experiments indicating that guinea pigs on a diet high in vitamin C developed marked sensitization reactions to neoarsphenamine, while pigs on low vitamin C diets developed a less marked sensitivity. Contrary to this, Sulzberger and Oser² reported marked sensitization reactions in scorbutic pigs. Cornua,³ also working experimentally with guinea pigs, showed that animals on low vitamin C diets had more intense initial skin reactions to neoarsphenamine than normal controls, and that involution of the lesions was slower. Although the experimental evidence seems to carry an implication, the experimental skin lesions at least are so different from the sensitizations seen in the clinical picture that comparison and evaluation are difficult.

Clinically, the application of this supposed relationship between vitamin C deficiency and arsenical sensitivity has been approached in a limited manner only. Damow⁴ reported beneficial results in treating arsenical dermatitis with ascorbic acid in three such cases. Landfisch⁵ observed loss of intolerance to neoarsphenamine in patients previously sensitive after the administration of vitamin C. Lever and Talbott,⁶ describing a group of miscellaneous forms of dermatitis treated with vitamin C, saw no improve-

* Received for publication December 5, 1949.

From the Department of Internal Medicine and Hygienic Laboratory for Medical Research, University of Kansas School of Medicine, Kansas City, Kansas.

ment in two cases of exfoliative dermatitis. It was, however, not stated that arsenic was the etiological agent in these two cases.

From this examination of the literature it seems evident that no attempt has been made to investigate intensively the possibilities of vitamin C as a clinical therapeutic agent in this group of complications of arsenical therapy.

Early but unorganized attempts to use cevitic acid in treating various forms of arsenical sensitivity at this clinic were made with inconclusive but promising results. In 1938 with a suitable method available for plasma vitamin C determinations, more careful observations were begun. One group of previously untreated syphilitics was selected in consecutive order, and vitamin C determinations were made upon the blood plasma. A second group was followed through routine arsenic and bismuth therapy courses with vitamin C determinations. A third group of selected cases was taken from patients showing definite arsenical sensitivity. These patients were followed with plasma vitamin C determinations during their therapy with cevitic acid*. The problem of selecting cases of unquestionable arsenical sensitivity soon became difficult when the entire group of such cases was pooled. Undoubtedly, the skin manifestations represent the ideal type for study. The time of onset is easy to determine, the patient's subjective progress is easy to follow, and the evidence of recovery cannot be controversial. All cases reported were either referred to the dermatological clinic for confirmation of the diagnosis or were seen in that clinic prior to their treatment in the medical department.

METHOD

The macro method of Mindlin and Butler⁷ was used for the vitamin C determination. The oxalated plasma was obtained and precipitated within 30 minutes after the blood was drawn. All bloods were obtained from patients who had not had any food for at least six hours.

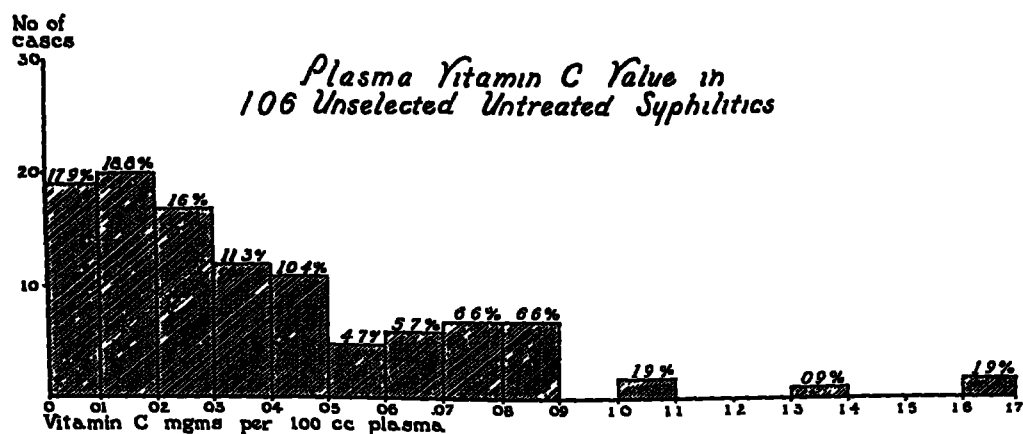


CHART 1 Consecutively chosen and previously untreated syphilitics showing plasma vitamin C levels

* Cevitic acid furnished by George A. Breon and Company

In this group of patients it may be seen that plasma vitamin C levels vary from less than 0.10 mg per 100 c c of blood to 1.4 mg. per 100 c c of blood. These represent levels much lower than those usually quoted. A preponderance of the group falls into what has often been called the scorbutic group. It should be pointed out that these patients were attending a charity clinic and that a diet adequate in fresh fruits and vegetables is practically unknown to them. The body weight as an indicator of the state of vitamin C saturation was an untrustworthy guide in this group. The great majority were diagnosed latent syphilis, however, several manifested primary and secondary lesions. No case complicated by other infectious disease was accepted for blood determinations.

Plasma Vitamin C (mg per 100 c c)

Patient Clinical No	Neocarsphenamine (Total dosage in gm)							
	0.0 gm	0.45 gm	0.9 gm	1.35 gm	1.80 gm	2.25 gm	2.70 gm	3.15 gm
151825	0.21	0.17	0.17	0.33	0.60	0.31	0.72	0.97
162131	0.08	0.05	0.20	0.26	0.13	0.20	0.19*	0.28
162166	0.04	0.12	0.05	0.09	0.36	0.05	0.45	0.70
162890	0.71	0.62	0.68	0.83	0.56	0.89	0.66	0.56
162069	1.64	—	1.26	1.64	0.90	1.06	0.96	1.01
162093	0.18	—	—	0.67	0.54	0.73	0.63	0.48
161967	0.09	—	0.23	0.17	—	0.33	0.04	0.30
162006	0.01	—	—	0.11	0.08	0.15	0.13	0.12
161909	0.14	—	—	0.07	—	0.36	0.37	0.20
158780	0.27	0.21	—	—	0.05	0.47	0.37	—
	(0.31)	(0.23)	(0.47)	(0.46)	(0.40)	(0.46)	(0.45)	(0.51)

Patient Clinical No	Bi-muth (Total dosage in mg metallic bi-muth)							
	0.0	1.30	2.60	3.90	5.20	6.50	9.10	10.10
161500	0.08	0.01	0.15	0.20	0.26	0.50	0.53	0.47
161679	0.05	0.37	0.02	0.11	0.17	0.24	0.10	0.23
161992	0.09	0.08	0.05	0.05	0.32	0.18	0.30	0.54
160778	0.11	0.51	0.74	0.89	—	0.62	0.60	0.59
151231	0.20	0.36	0.31	0.35	0.05	0.85	0.64	0.26
162171	0.49	—	0.22	0.36	0.31	0.11	0.50	0.35
163281	1.01	—	0.83	—	0.90	—	—	0.53
162370	0.26	—	0.21	—	0.12	—	0.55	0.55
161703	0.25	—	0.05	—	0.05	—	0.35	0.32
162812	0.13	0.12	0.11	0.26	0.26	0.21	0.46	—
	(0.30)	(0.25)	(0.27)	(0.32)	(0.27)	(0.47)	(0.45)	(0.43)

* Dermatitis developed

CHART 2 Plasma vitamin C level before and during routine administration of arsenic and bi-muth

The group shown in chart 2 represented unselected patients, previously untreated, followed for the purpose of determining the presence or absence of a depressing effect of the heavy metals administered upon the plasma vitamin C level. No such depressing effect is noted. The dietary histories of

these patients indicated clearly a close relationship between the intake of vitamin C and the vitamin C plasma levels

ARSENICAL DERMATITIS TREATED WITH CEVITAMIC ACID

The last individually studied group represents five patients with unquestionable arsenical dermatitis. Each was treated with cevitic acid as indicated in the accompanying summaries and charts. Plasma vitamin C levels were determined before treatment was started and throughout the course of

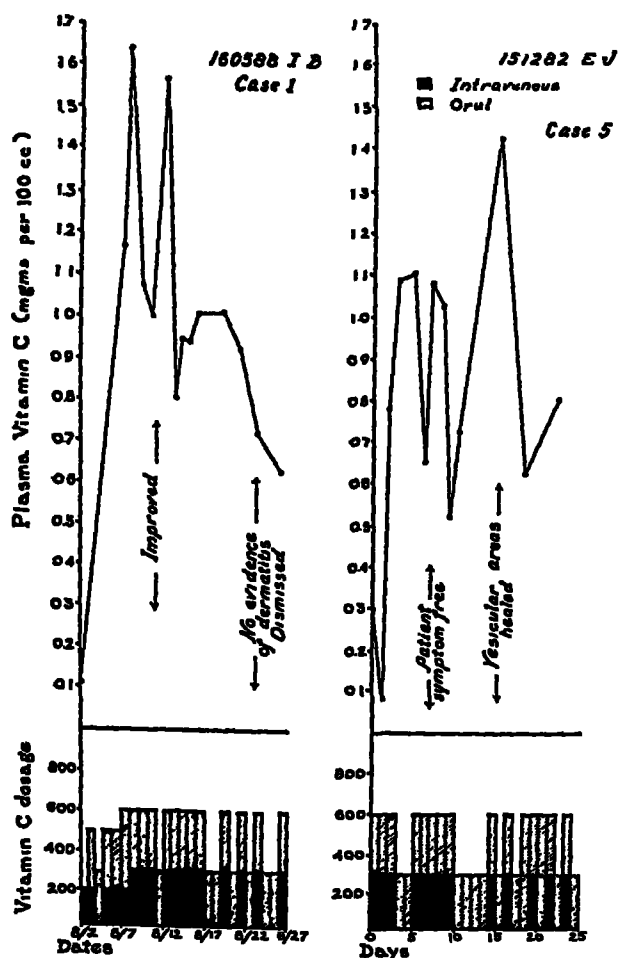


CHART 3 Case 1 and Case 5

treatment. All patients were treated as ambulant cases, and no therapy other than vitamin C orally and intravenously was administered. Patients were secured from several sources, but all represent a group in clinical classification. Only one patient, case 2, appears in groups one and two. She had vitamin C determinations made before and during routine arsenical therapy. As a group these cases show low vitamin C values, but even in case 2 it is not possible to say that the arsenic therapy had depressed the level to a point where sensitization appeared.

CASE REPORTS

Case 1 I B Female, white, aged 32 Entered the medical clinic with complaints of nervousness, stomach trouble, and a positive Wassermann test Significant in the past history were eight pregnancies with three premature labors, and frequent attacks of upper abdominal pain The patient was poorly nourished, and had a very severe gingival infection Otherwise, the physical findings were negative Roentgen-ray examination with oral dye showed a non-functioning gall-bladder This patient,

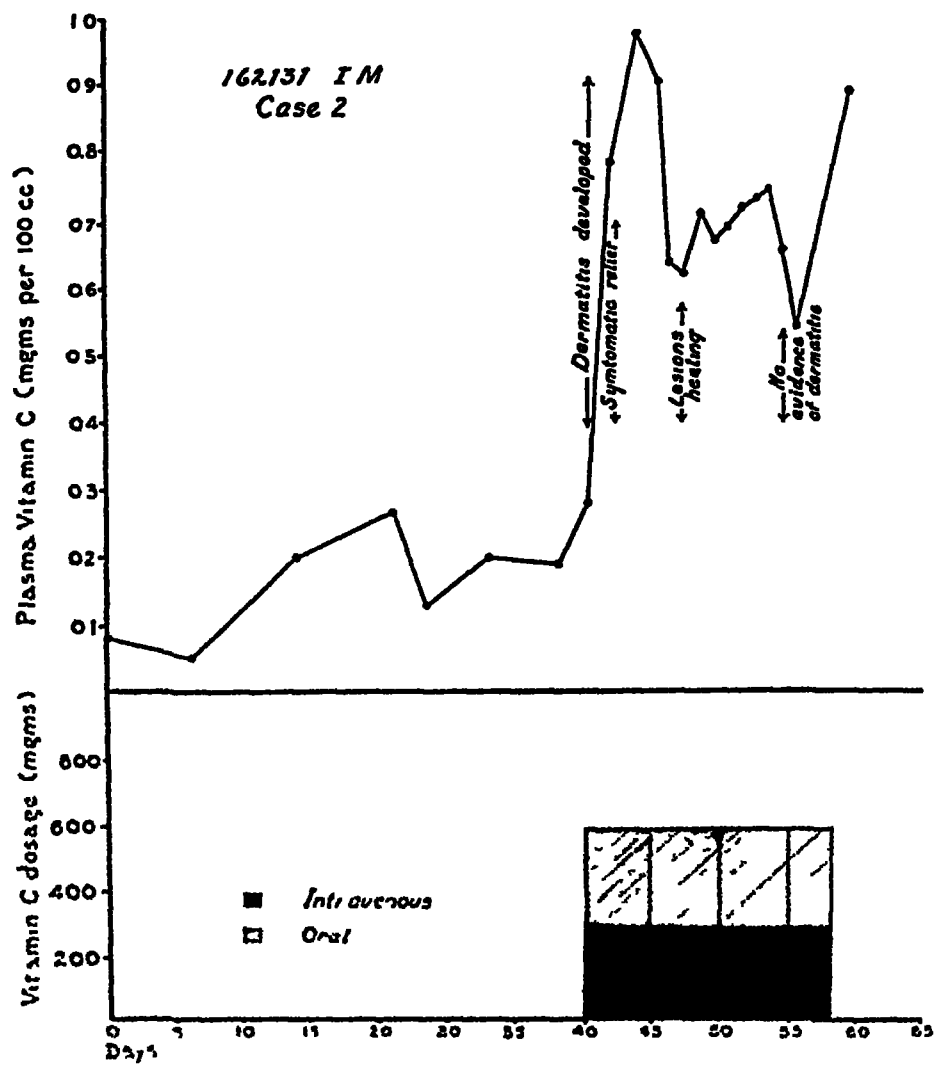


CHART 4 Case 2

three children and the husband, living on direct relief, had a weekly allotment of \$1.85 for food, consequently intake of fruits and fresh vegetables was negligible

After one course of bismuth emulsion consisting of 20 injections of 1 cc each, the patient was placed on neosporamine Following the seventh dose she developed a generalized vesicular eruption particularly intense on the skin of the face, neck, ears, arms, hands, and trunk The dermatitis had been present for four days at the time reported At this time the patient was placed on ascorbic acid, both intravenously and orally Within one week the patient was definitely improved Within three weeks all evidence of dermatitis had disappeared

Case 2 I M Female, colored, aged 25 Admitted to the medical clinic with the chief complaint of "Bad Blood" The patient and her family were on direct relief

and very rarely had any fresh vegetables in their diet. The past history was unimportant. Physical findings were not significant. The medical diagnosis was sero-positive latent syphilis.

This patient was placed on neoarsphenamine with an initial dose of 0.3 gram and subsequent doses of 0.45 gram. In this patient plasma vitamin C determinations were being made throughout the course of treatment. Following the seventh injection of neoarsphenamine, the patient developed a typical generalized arsenical dermatitis with marked edema and vesiculation of the skin of the face, ears, neck, extremities, and trunk.

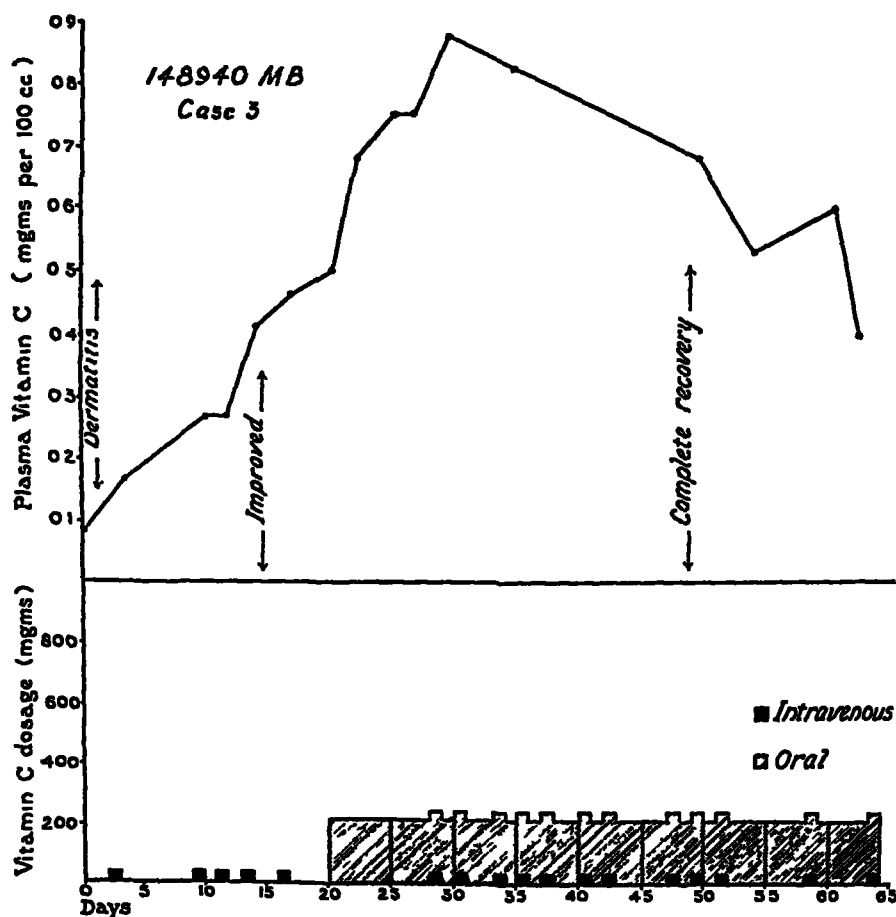


CHART 5 Case 3

The third day following the onset of the dermatitis, both intravenous and oral cevitamic acid therapy was begun. Within 48 hours the patient had complete relief from the intense burning and itching of the skin, within seven days there was definite healing of the vesiculations, within 14 days the dermatitis had completely disappeared. No other treatment was given during the course.

Case 3 M B Female, colored, aged 34. Entered the medical clinic with the chief complaints of nervousness and palpitation. Routine examination revealed that the patient had a positive Wassermann test, but no other significant findings. The family was on direct relief and records of other members of the family indicated definite lack of proper nutrition.

The patient was referred for syphilitic therapy and she received one course of neoarsphenamine, one course of bismuth, and six injections of neoarsphenamine in her

second course of treatment, at which time she developed a typical arsenical dermatitis with generalized involvement of the skin. Treatment with cevitic acid intravenously was begun. The patient received 50 mg doses three times weekly. Although we now know the dosage to be quite inadequate, at the end of two weeks' time the patient was showing very definite improvement. She did not show complete recovery until seven weeks had elapsed. It was quite impossible to persuade the patient to take daily doses of medication, and sometimes there were intervals of one week between treatments.

Case 4 W W Male, colored, aged 38. This patient entered the dermatological clinic with the chief complaints of burning skin and dermatitis. Onset of the illness had occurred two months previously following the sixth intravenous injection of neo-

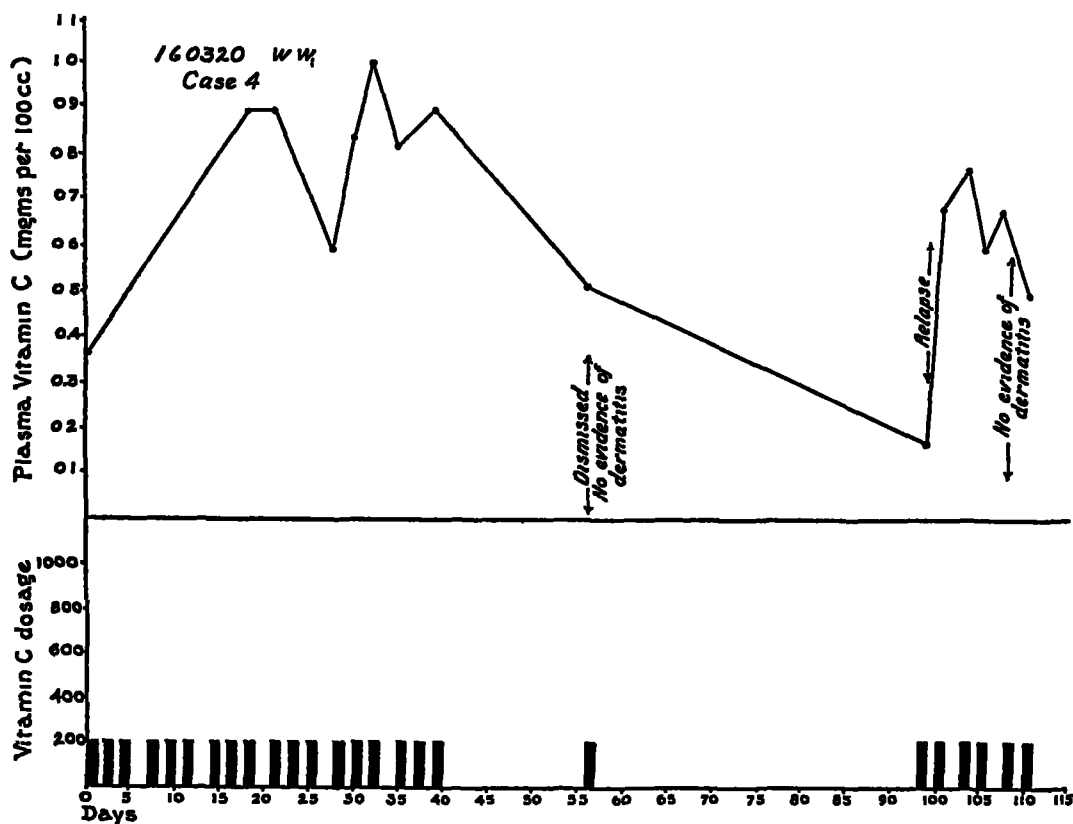


CHART 6 Case 4

arsphenamine. The patient was not syphilitic, and had been receiving the medication, apparently, for its tonic value. The history did not reveal any inadequacy in the patient's diet. During the two months intervening since the onset, the patient had used many ointments without benefit. A diagnosis of arsenical dermatitis was evident.

This patient was placed on intravenous cevitic acid in doses of 200 mg three times weekly. After the sixth dose, the patient showed improvement and was free from the intense burning and itching. With the twelfth dose the dermatitis disappeared. After the nineteenth dose, the patient was dismissed, but returned five weeks later with a mild recurrence. Medication was resumed with a prompt remission. He was again dismissed. Three weeks following his second dismissal he had another mild recurrence which was promptly controlled upon resumption of the cevitic acid medication.

Case 5 E J (see chart 1) Male, colored, aged 18. This patient was admitted to the dermatological clinic with the chief complaints of burning and itching

of the skin. The dermatitis had been present one week, and followed the fifth dose of neoarsphenamine in his third regular course. The patient's nutritional state was good. In addition to syphilis the patient had an active gonorrheal proctitis. The diagnosis was typical arsenical dermatitis of an extremely severe type. Skin involvement was very extensive and associated with marked subjective symptoms. Cevitamic acid therapy, both intravenously and orally, was begun immediately. No other treatment was given. On the seventh day of treatment the patient was free of all the burning and itching of the skin, and all the edema had vanished. Slight vesiculation still remained. By the fourteenth day of treatment the patient was completely symptom free. All vesiculation had disappeared. However, his treatment was continued for fear of relapse.

DISCUSSION

It seems likely that our conception of normal vitamin C values needs downward revisions. In the 106 patients studied previous to the administration of antisyphilitic therapy, values ranging from less than 0.10 mg per 100 c.c. of blood to 1.4 mg per 100 c.c. of blood were found. Fifty per cent are below 0.4 mg. No patient evidenced clinical scurvy, yet the values are definitely within the assumed range for such a state. Lever and Talbott⁶ found in a group of healthy medical students and nurses 11 per cent showing vitamin C values less than 0.3 mg. Seven out of eight of their patients with exfoliative dermatitis had vitamin C values less than 0.3 mg. Friend and Marquis⁸ reported the vitamin C level in one case of arsenical dermatitis at 0.13 mg per 100 c.c. of blood. Croft and Snorf⁹ found 38 per cent of a group of medical patients with vitamin C values less than 0.4 mg per 100 c.c. of blood. Compared with these available figures the values in this studied group do not seem abnormally low.

No explanation has been made in the past for what is supposed to be relationship between vitamin C deficiency and arsenical sensitivity. None can be offered here for what seems to be a beneficial effect from vitamin C administration in arsenical sensitivity. The problem requires more extensive clinical observation and deeper probing into the basic problems.

There is still no proof for the belief that a method is available for selecting by routine plasma vitamin C determinations a patient who will develop arsenical sensitivity. Case 2, by chance, was being followed at the time of the appearance of the sensitization, but her values had been consistently low. It cannot be said that the arsenic had produced any loss in vitamin C level, yet she improved dramatically with a forced rise in plasma vitamin C levels. The significance is not clear.

While all cases of dermatitis studied show low vitamin C values, the disease was manifest at the time of the determinations. The low values do agree with meager information available in the literature.

Contrary to the findings of Farmer, Abt, and Arons¹⁰ the cases in this group receiving arsenic show nothing which can be interpreted as a depressing effect of arsenic upon the vitamin C levels. Our results agree with theirs in regard to bismuth.

Case 4 is interesting in that the height of his vitamin C level apparently paralleled his state of well-being. Twice, when therapy was stopped vitamin C values dropped, and simultaneously the patient relapsed with a return of his dermatitis. Voluntarily, the patient returned requesting more vitamin C.

No cases have been treated exclusively with oral medication, so no opinion is justified, but the impression has been gained that intravenous administration is the procedure of choice. Dosages in the cases studied have varied with earlier cases getting smaller doses as indicated, and later cases receiving up to 300 mg intravenously daily. Larger doses may be justified.

SUMMARY

One hundred and six cases of untreated syphilis showed vitamin C levels consistent with their dietary intake of vitamin C. No change in the curve of plasma vitamin C levels was noted in either group of patients receiving the metals arsenic or bismuth. A group of five cases manifesting arsenical sensitivity was studied. Although patients developing sensitivity had low vitamin C values, a low vitamin C value does not necessarily predict such an outcome. Cases of arsenical dermatitis treated with cevitamic acid showed sufficiently favorable response to warrant further employment and study of cevitamic acid therapy.

BIBLIOGRAPHY

- 1 CHAPMAN, C W, and MORRELL, C A. Influence of vitamin C on the development of skin sensitivity to neoarsphenamine in the guinea pig, *Proc Soc Exper Biol and Med*, 1935, **xxxii**, 813-815.
- 2 SULZBERGER, M B, and OSER, B L. The influence of ascorbic acid of diet on sensitization of guinea pigs to neoarsphenamine, *Proc Soc Exper Biol and Med*, 1935, **xxxii**, 716-719.
- 3 CORMIA, F E. Experimental arsphenamine dermatitis—the influence of vitamin C in the production of arsphenamine sensitiveness, *Canad Med Assoc Jr*, 1937, **xxxi**, 392-396.
- 4 DAINOW, I. Desensitization action of l-ascorbic acid, *Ann Dermat and Syph*, 1935, **vi**, 830.
- 5 LANDFISCH, S. Redoxon in prophylaxis of arsphenamine accidents, *Polska. gas lek*, 1937, **xvi**, 575-577. Synthetic cevitamic acid—new auxiliary remedy in arsphenamine therapy, *Jr Am Med Assoc*, 1937, **cix**, 834.
- 6 LEVER, WALTER F, and TALBOTT, JOHN H. Role of vitamin C in various cutaneous diseases, *Arch Dermat. and Syph*, 1940, **xl**, 657-663.
- 7 MINDLIN, R L, and BUTLER, A M. Determination of ascorbic acid in plasma. Macro-method and micromethod, *Jr Biol Chem*, 1938, **cxii**, 673-686.
- 8 FRIEND, DALE G, and MARQUIS, HAROLD H. Arsphenamine sensitivity and vitamin C, *Am Jr Syph, Gonorr and Ven Dis*, 1938, **xxii**, 239-242.
- 9 CROFT, JOSEPH D, and SNORF, LOWELL D. Cevitamic acid deficiency frequency in a group of 100 unselected patients, *Am Jr Med Sci*, 1939, **cxcviii**, 403-408.
- 10 FARMER, CHESTER J, ABT, ARTHUR F, and ARONS, HANS C S. Influence of arsenicals, bismuth and iron on plasma ascorbic acid level, *Proc Soc Exper Biol and Med*, 1940, **xli**, 495-499.

CASE REPORTS

LONG STANDING PRODUCTIVE COUGH AS CHIEF CLINICAL MANIFESTATION IN MITRAL STENOSIS; A CASE COMPLICATED BY THROM- BOSIS OF LEFT AURICLE*

By ESTELLE E KLEIBER, M D, *New Brunswick, N J*

IN most cases of mitral stenosis with failure, cough is one of a number of symptoms in few does it overshadow all others. It may be due to chronic congestive catarrh of the bronchial mucosa, but in the case reported below the mildness of the pulmonary changes offered no explanation of the cough. Indeed in this case the absence of marked pulmonary congestion is a crucial point since it aids in establishing the fact that severe and productive cough in this condition can be due merely to the mechanical pressure of an enlarged auricle on the trachea and bronchi.

CASE REPORT

The patient, a 52 year old housewife, was first seen at the Middlesex Hospital Cardiac Clinic, where she was admitted on February 2, 1935 with the chief complaint of severe paroxysmal cough. Her mother had died of "heart disease and asthma." The patient had had rheumatic fever at 19 years and frequent joint pains thereafter. Menopause occurred at the age of 44. She was married for 34 years and had borne eight children, besides having two miscarriages.

In 1934 (one year before admission to the clinic), she had first noted cough, dyspnea on exertion, orthopnea requiring three pillows at night, and loss of weight. The cough was severe and came in paroxysms. For several weeks it had been accompanied by expectoration of thick tenacious mucus. The attacks were more frequent at night. For this condition the patient was admitted to the Middlesex Hospital where she remained for 30 days. Rheumatic heart disease with mitral stenosis and auricular fibrillation was found. She was treated by bed rest, digitalis and ephedrine. Both nurses' and internes' notes recorded the severe exhausting cough and "continuous expectoration." At this time impaired resonance was noted at both bases and throughout both lung fields anteriorly and posteriorly, numerous sibilant and sonorous râles were present. Stereoscopic radiographs were taken of the chest on December 26, 1934. The report was as follows: "The apices aerate fairly well. The appearance is that of generalized fibrosis of both lung fields with some pulmonary edema and pleural effusion in the left base. There is no evidence of pulmonary tuberculosis. The heart is mitral in type. There is a suggestion of bronchiectasis in the right base."

On physical examination we observed a middle-aged woman in a poor state of nutrition, weight 125 pounds, temperature 98.4° F. Skin and mucous membranes were pale but not cyanotic. All teeth had been removed. The neck showed no masses and

* Received for publication September 25, 1940.

From the Middlesex Hospital Cardiac Clinic and from the Medical Service and Pathological Laboratory of St. Peter's Hospital, New Brunswick, New Jersey.

no abnormal pulsations The heart was enlarged to the left with the apex impulse in the anterior axillary line The sounds were weak, irregular, rapid and no murmurs were detected on this examination Later a long, rumbling diastolic murmur was heard in the mitral area and a short systolic one in the left third and fourth interspaces The second aortic and pulmonic sounds were equal Peripheral vessels were somewhat sclerotic The blood pressure was 120 mm of Hg systolic and 80 mm diastolic The chest showed dullness at the apices, especially on the right, but no râles were present The abdomen was slightly distended and the musculature flabby The liver was not enlarged Fluoroscopic examination showed a generally enlarged heart with fullness along the left border in the region of the pulmonic conus and left auricle Enlargement of the right auricle was suggested by the increase of the heart shadow to the right of the midline

The urine was acid, specific gravity was 1.011, there was a trace of albumin, but no sugar, an occasional white blood cell was seen microscopically The Wassermann test was negative The hemoglobin was 68 per cent (Sahli), red blood cells 3,860,000, white blood cells 7,400, polymorphonuclears 70 per cent, lymphocytes 22 per cent, eosinophiles 2 per cent, and basophiles 1 per cent The sputum examination was negative for tubercle bacilli and for blood

The diagnosis made was as follows

- (1) Rheumatic heart disease—inactive
- (2) Mitral stenosis and insufficiency with enlargement of both auricles
- (3) Auricular fibrillation
- (4) Possible bronchiectasis and lung fibrosis

Following the first clinic visit, the patient had an upper respiratory infection and with it came increased cough which was so severe as to cause loss of appetite and several episodes of vomiting This symptom was not helped by cough syrups but subsided with rest in bed and digitalis In May 1935 the cough returned and the patient noted blood-streaked sputum for the first time Her heart rate was controlled by digitalis at approximately 76, without pulse deficit She was free from other symptoms During the next two years, the patient remained ambulatory and had short periods free from cough interspersed with others when this symptom was severe She was treated with potassium iodide solution, with ammonium chloride, and with various cough mixtures, besides the daily maintenance dose of 0.1 gram of digitalis

In June 1937 cough and expectoration were again troublesome Postural drainage was unsuccessful The patient was referred for bronchoscopic examination and treatment The bronchoscopist reported that the case appeared to be "an early stage" of bronchiectasis without evidence of any dilatation of bronchi Mucus was removed by lavage and the patient felt clinically improved so that she requested further treatment Expectoration stopped for three months A total of seven bronchoscopic treatments was given during the next six months, thereafter the patient refused such treatments as she felt weakened thereby

In June 1938, edema of the legs was first noted As the patient had severe varicosities, these were thought to account for at least part of the swelling Râles were present at the left base The patient was urged to remain off her feet and digitalis was increased to 0.2 gram daily, since the pulse rate varied from 88 to 100 per minute After temporary improvement, edema of the legs again became marked in January 1939, and was accompanied by severe dyspnea, by orthopnea and by cyanosis The cervical veins were engorged Coarse râles and dullness were present at both bases, the heart was irregular (120) with pulse deficit Sacral edema was also present The patient was again admitted to Middlesex Hospital and a diagnosis of congestive failure made Urea nitrogen was 14.1 mg per 100 cc of blood, sugar 121 mg Salyrgan was given intravenously every two days, and with limited fluids and ammonium chlo-

ride the patient became free from evidence of fluid retention and lost 20 pounds. After a brief remission during which the patient felt well, congestive failure again became evident in March 1939. Again she improved after hospitalization, but cough remained troublesome.

An electrocardiogram on January 1, 1940, showed auricular fibrillation, rate 100, QRS 008, right axis deviation, widening and notching of QRS in Lead I and Lead II; ventricular premature contractions in Lead III, T₁ and T₂ upright and T₃ and T₄ diphasic. Circulation time with saccharin was 26 seconds (normal 9-16 seconds). Again the cough was the only complaint during the clinic visits, usually with sputum, occasionally blood tinged. The nurses and physicians of the clinic learned to recognize her coming long before seeing her, because of the loud and nearly continuous cough which heralded her presence. In April 1940, edema of the legs again became marked in spite of the weekly dose of salyrgan.

On July 9, 1940, she walked several blocks to the clinic which she reached by great effort. Her color was ashen gray, and her lips, ears and fingers were markedly cyanotic. She had massive pitting edema of the legs, and was extremely dyspneic and orthopneic. Her pulse was weak, rapid and irregular, and blood pressure readings could not be obtained in either arm. A gallop rhythm was present at the apex. She was admitted at once to St. Peter's Hospital in a moribund condition and she died six hours later.

Autopsy was performed by Dr. S. E. Moolten, pathologist.

AUTOPSY PROTOCOL

The subject was described as a poorly developed female of 53 showing marked lividity of dependent parts and head. There was considerable soft pitting edema of the lower extremities and sacrum. There was a faint purpuric mottling of the skin of the legs. There was no clubbing of the fingers and no jaundice.

Lungs Both lungs were adherent over part of their surface especially the left lung which was densely adherent to the diaphragm and fibrous pericardium. The lungs were somewhat firmer than normal in consistence, and on section showed only slight hyperemia of dependent portions. The lowest part of the right lower lobe was somewhat indurated and on section presented a somewhat more anthracotic appearance than the remaining lung and seemed slightly more airless. A similar change was seen in the lower part of the left lower lobe. The remaining tissue was more crepitant throughout and was fairly dry and pale, showing minimal congestion and no significant edema. The trachea was of normal size. However, the right main bronchus was somewhat wider than normal for a short distance and the left main bronchus was slightly diminished in caliber and seemed somewhat elongated. The distance from the carina to the orifice of the right upper lobe bronchus was 2.5 centimeters and from the carina to the left upper lobe bronchus was 4.5 centimeters. The right main bronchus was approximately 1.7 centimeters in diameter and the left main bronchus 1.2 centimeters. The branches of the right main bronchus appeared normal throughout. Those of the left main bronchus seemed somewhat narrowed as far as they could be dissected and the orifices were somewhat flattened from before backwards in contrast to those of the right bronchus. The mucosa was pale and smooth and of normal appearance. The tracheo-bronchial angle was greatly exaggerated measuring approximately 135°. This was the result of changes in the left auricle which will be described below (figure 1).

Heart The pericardial cavity was completely obliterated by fibrous adhesions. The outer layer of the pericardium was similarly bound by fibrous adhesions to the overlying lungs anteriorly and laterally, by obliteration of the intervening pleural space in this region. The soft tissues of the upper mediastinum were somewhat thickened. The heart was greatly enlarged as a result of a marked degree of dilatation and a

fairly marked degree of hypertrophy. The wall of the right ventricle was nearly one centimeter thick. The right auricle was also markedly dilated and its endocardium was thickened and more or less opaque and white. The right auricular appendage was somewhat contracted and flattened and contained no thrombi. The superior and inferior vena cavae were somewhat dilated in a uniform manner. The auricular myocardium was moderately atrophic except in its lowest portion where it was hypertrophic. The tricuspid valve showed a moderate degree of hyaline thickening, especially along the line of closure, with some retraction. The chordae tendineae were, for



FIG 1 Specimen showing widening of tracheo-bronchial angle and enlarged left auricle with thrombus. Note the slit-like mitral orifice.

the most part, considerably shortened and thickened with a considerable degree of fusion near their attachment, and the papillary muscles were shortened. There was a pronounced degree of valvular incompetence. The pulmonic valve appeared grossly normal. The pulmonary artery was smooth and free of atheroma. The left auricle, before opening, could be felt as a peculiar hard tumor mass just beneath the bifurcation of the trachea. When opened this effect was seen to be the result of an adherent mural thrombus occupying the upper two-thirds of the auricular cavity and extending for a short distance into the lumen of the left upper pulmonary vein, causing marked narrowing but not obstructing it completely. The thrombus, in large part, was pale flesh color and gray especially in the deepest portions. It could be separated from its attachment to the auricular endocardium revealing the latter as greatly thickened and somewhat roughened. The auricular myocardium in its upper part was moderately atrophied. In its lower part it was greatly hypertrophied and reached 0.75 centimeter in thickness. There were numerous areas of whitish plaque-like endocardial thicken-

ing and wrinkling throughout the left auricle where it was not in contact with thrombus. The mitral valve was extremely narrow and reduced to a slit about one centimeter long and a few millimeters wide. The mitral leaflets were moderately thickened and hyalinized with areas of calcification. The chordae tendineae were extremely short, thick, and fused and the papillary muscles were elongated and thickened with fibrosis of the tips. The left ventricle was of normal appearance on section and its endocardium appeared unaltered, the wall was of normal thickness and the cavity contracted. The aortic valve cusps were moderately thickened and the edges were fairly rigid producing a moderate degree of insufficiency. There were no vegetations except a tiny area of projecting fibrinous material on one of these cusps. The aorta was smooth and elastic and presented scattered areas of slight atherosclerosis and was slightly dilated in its ascending portion. The coronary vessels were somewhat diminished in calibre but smooth and free of obstruction.

Liver The liver appeared slightly contracted rather than enlarged. The surface showed somewhat exaggerated venous markings and was finely granular with considerable wrinkling. It cut with some difficulty revealing considerable exaggeration of the lobules throughout. Some of these were two to three times normal size and others were much smaller. The interlobular tissue was slightly exaggerated and had a pale translucent aspect. The centrilobular areas appeared considerably reddened but most of the blood had run out of the organ. In many of the lobules fine yellow granular areas could be detected on gross inspection. The lobules in general were quite yellowish. The hepatic veins were widely patent and appeared slightly thickened. The portal vein was also slightly thickened and showed slight plaque-like opacities at branchings. The gall-bladder was contracted firmly about a number of small black faceted pigment calculi. There was considerable cholesterosis of the gall-bladder mucosa. The hepatic and common bile ducts were slightly widened in a uniform manner and contained no calculi.

Pancreas The pancreas was rather firm. The cut section was negative.

Spleen The spleen weighed 230 grams, was enlarged to a moderate degree and was very firm. It had a rubbery consistence and showed a dark brownish-red cut surface with somewhat exaggerated venous markings. The splenic vein was patent and smooth.

Adrenals Negative.

Kidneys Both kidneys were of normal size and were smooth. The capsules stripped readily revealing a slightly congested surface with a few small irregular flat stellate scars extending slightly beneath the surface. On cut section the parenchyma was somewhat congested and firm. The pelves, ureters and bladder were negative. The kidneys together weighed 440 grams.

Genitals The vagina was smooth and atrophic. The external os of the cervix was occluded by a mucus plug and a fibroadenomatous polyp. The cavum uteri showed atrophic endometrium with superficial hemorrhage. The myometrium was atrophic. The ovaries were shrunken and fibrotic.

Diagnoses

- 1 Chronic recurrent cardiovascular disease, rheumatic, with extreme mitral stenosis and moderate aortic insufficiency (Aschoff bodies present)
- 2 Marked tricuspid insufficiency
- 3 Universal adhesion of pericardium
- 4 Adherent thrombus of left auricle causing marked reduction of lumen
- 5 Elongation and narrowing of left main bronchus
- 6 Marked dilatation and hypertrophy of the right ventricle
- 7 Marked dilatation of the right auricle
- 8 Chronic passive congestion of liver, spleen and gastrointestinal tract

- 9 Adenomatous regeneration of hepatic lobules
- 10 Stasis catarrh of stomach
- 11 Cholelithiasis
- 12 Bilateral pleural adhesions
- 13 Fibrous induration and atelectasis of basal areas of both lungs
- 14 Anasarca

HISTOLOGY

Heart Section through auricular thrombus thrombus composed of eosin-staining amorphous substance, with numerous areas of spongy rarefaction alternating with more or less homogeneous areas, the latter generally showing a definite lamination. Considerable hyalinization of deepest areas abutting on endocardial region. Attachment of thrombus to auricular wall was marked by irregular collections of hemorrhage, old and recent, within dense hyaline avascular tissue resembling dense collagenous tissue which merged insensibly with overlying hyalinized thrombus. Still deeper

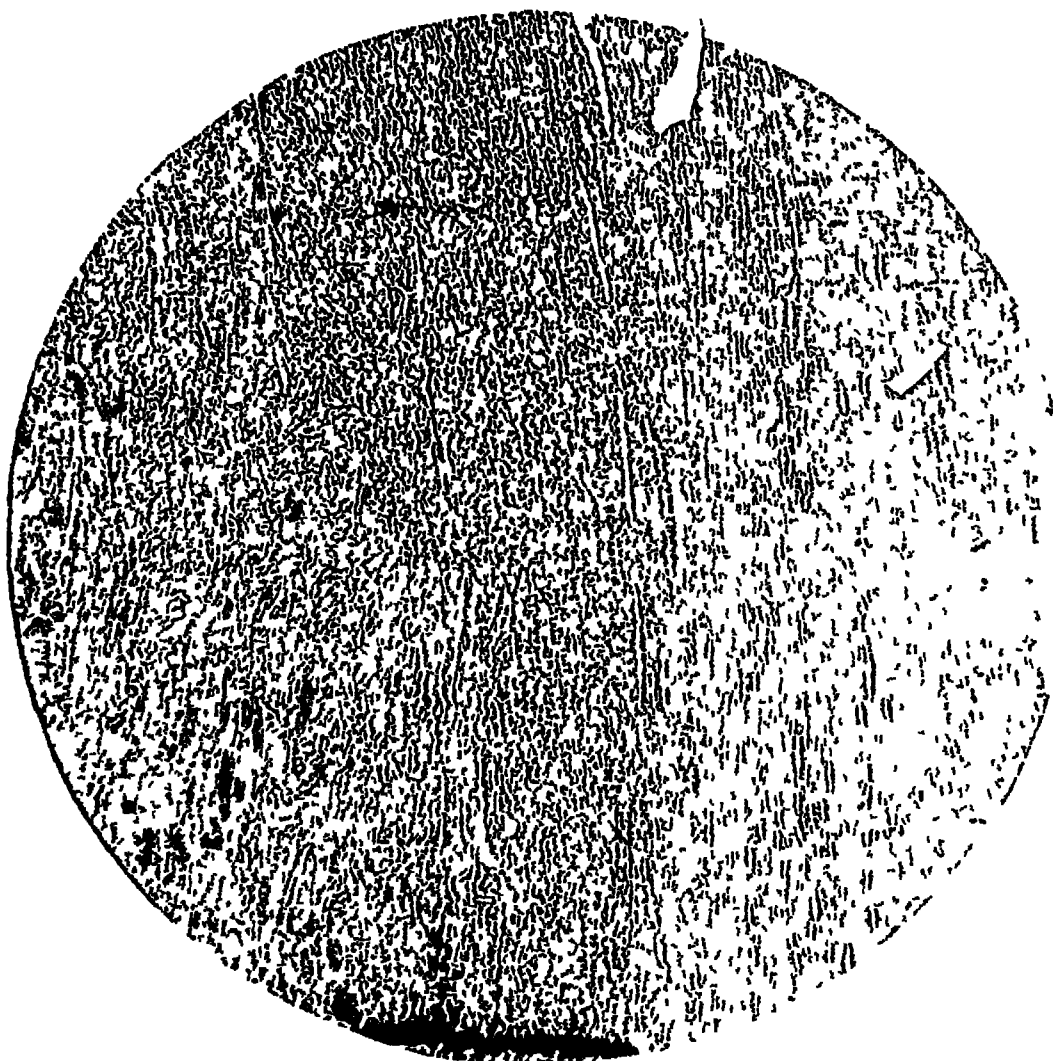


FIG 2 Section of wall of left auricle showing extensive fibrosis and hyalinization of subendocardial region with considerable replacement of myocardium. Note discontinuity and distortion of remaining muscle fibers.



FIG 3 Recent Aschoff granuloma within myocardium of left ventricle

the structure of the collagenous fibrous tissue was more evident as such but showed considerable degeneration, so that many cell nuclei were replaced by empty clefts, others appeared shrunken and pyknotic. This was most marked in a strip overlying a still deeper hemorrhage within the subendocardial fibrous tissue which was of considerable thickness. There was no differentiation into endocardium and subendocardium as such and no endothelial layer could be defined. The dense layer of fibrosis occupies the greater part of the thickness of the auricular wall, and the auricular muscle was discontinuous and largely degenerated except for scattered islands of shortened thickened fibers irregularly disposed and with bulky hyperchromatic nuclei.

(figure 2) There was a slight irregular infiltration of this layer with lymphocytes and a variable degree of congestion. The epicardium was considerably thickened by dense fibrous tissue forming a more or less continuous layer, apparently the result of adhesion with the parietal pericardium. Sections through both ventricles and the right auricle showed a few recent Aschoff nodules (figure 3) as well as a number of small areas of scarring representing healed Aschoff nodules, the fibers of the right ventricle and auricle showed well-marked hypertrophy.



FIG 4 Section of lung showing marked narrowing of branches of pulmonary artery by intimal fibrous hyperplasia. Note patchy atelectasis and thickening of alveolar septa but surprising absence of congestion and edema.

Lungs The most striking changes in the lungs were the evidences of previous marked chronic passive congestion and the relative lack of congestion at the present time, also the hypertrophy of the intrinsic muscle of the lung and the narrowing of arteries. Previous chronic passive congestion was seen in the form of thickening of alveolar septa as a result of increase in fibrillar reticulum, together with moderate contraction of the alveoli and considerable hypertrophy of the muscularis of the alveolar ducts about the orifices of the alveolar sacs. Numerous areas of old atelectasis were seen with partial fusion of alveolar septa and here the muscle fibers appeared

shortened and thickened and gave rise to the appearance of "muscular cirrhosis" In some sections numerous "heart failure cells" were seen within the atelectatic areas or lining the walls of other alveoli, these contained old blood pigment and anthracotic pigment and often appeared degenerated, in some areas they were secondarily engulfed by multinucleated foreign body giant cells formed by more recent proliferation of alveolar epithelium The latter was often somewhat hyperplastic, forming rows of cuboidal epithelium in and about areas of atelectasis Very striking was the lack of blood in the alveolar capillaries many appearing collapsed and bloodless, others showing only small numbers of erythrocytes, the usual appearance of scalloped projecting capillary outlines engorged with blood was entirely lacking, moreover nowhere was there to be seen any trace of edema fluid or other exudation The small and medium size arteries showed moderate to marked intimal fibrous thickening with resulting narrowing of lumen, often very marked, the internal elastica seemed somewhat thickened and reduplicated A few nodules of lymphoid character were seen here and there but no other evidence of leukocytic infiltration Carnification also was not seen Bronchi contained some mucus (figure 4)

Liver Considerable chronic passive congestion with thickening of reticulum framework and mild centrilobular degeneration were noted, there was marked intimal fibrous hyperplasia with narrowing of lumen of branches of the hepatic artery, Glisson's capsule presented considerable fibrosis with subcapsular atrophy and fibrous replacement of lobules

Spleen Marked chronic passive congestion with thickening of reticulum framework and beginning fibrosis of pulp cords were noted

Adrenal The sinusoids of the cortex and of the medulla showed considerable congestion, the cells were well formed and the layers were of normal proportions, there was slight patchy degeneration of cortex, the surrounding fat tissue showed foamy condensation as seen in fat resorption

Kidney The kidney showed uniform congestion of cortex and medulla, glomeruli were numerous, well formed, and congested, Bowman's space was somewhat dilated but free of exudate of cells or protein, the arterioles and small arteries showed no significant changes

Stomach There was moderate hypoplasia of the mucosal glands with scattered areas of slight hyperplasia and diffuse congestion and edema of the stroma, there was mild infiltration of the stroma with lymphocytes and plasma cells, also of the submucosa and of the muscularis

COMMENT

The left auricle constitutes most of the posterior portion of the heart The bifurcation of the trachea and part of the left main bronchus lie just above it Unusual degrees of enlargement of this chamber have been reported in mitral valvular disease associated with marked insufficiency or stenosis and where extensive rheumatic carditis is present in the auricular muscle By compression of neighboring structures, a number of unusual secondary effects may present themselves clinically

(1) The upward displacement of the left main bronchus and pulmonary artery may compress the left recurrent laryngeal nerve in its course beneath the arch of the aorta resulting in paralysis of the left vocal cord This gives rise to hoarseness and "brassy cough" as in the cases of left ventricular failure reported by King, Hitzig and Fishberg¹ In such cases the lungs may be remarkably free of signs of congestion clinically although the pulmonary veins appear markedly engorged roentgenologically Hoarseness was not observed in the present case nor were the vocal cords described as abnormal by the bronchoscopist

(2) Compression of the esophagus in the middle portion of its course behind the left auricle may cause some degree of difficulty in swallowing. In five such cases reported by Nichols and Ostrum² dysphagia was a prominent symptom, in one case a tumor of the esophagus was suspected and the patient subjected to gastrostomy. Cough was mentioned in four as one of many symptoms but was not especially prominent. These authors emphasize the relative freedom from congestive heart failure in these cases. A recent publication discusses the occurrence of dysphagia in a variety of disorders of the circulatory system—among them the dilated left auricle.⁹

(3) The chief effect of the dilatation of the left auricle may be seen in the compression of the left main bronchus and widening of the tracheo-bronchial angle as in the case reported above. With such enlargement, the auricle may act as a wedge penetrating the tracheal bifurcation and producing a widening of the angle from the usual range of 50 to 80 degrees to as much as 150 degrees. In this process the bronchi, especially the longer left one, may become considerably compressed. Cough may be an outstanding symptom because of the mechanical irritation of this sensitive portion of the bronchial tree. According to Steele³ bronchial compression by an enlarged left auricle has been known for nearly a century. Rarely it is sufficiently marked to produce atelectasis of the left lung and chronic inflammation with bronchiectasis. He reviewed the literature from 1838 and presented a case resembling the author's in the severity of the cough, the presence of sputum with blood spitting and the long duration of symptoms (5 years). Here too, bronchiectasis of the left base was suspected, however, on lipiodol injection this was disproved and the distortion of the left main bronchus demonstrated.

Routier and de Balsac^{4,5} presented the radiological findings in such cases and Graybiel⁶ reviewed the mechanism of its production.

In the author's case the cough was known to have been present for over six years and was usually productive of mucoid or muco-purulent sputum which was occasionally blood tinged. In the beginning most attacks were initiated by an upper respiratory infection but later persisted without relation thereto. During most of this time the patient was ambulatory and otherwise comfortable, with remarkably good exercise tolerance and relative freedom from signs of congestive failure. The angle at the bifurcation was found at autopsy to be 135 degrees, although the degree of auricular enlargement was not excessive. Clinically the diagnosis of bronchiectasis was considered because of the violence and persistence of the cough, the amount of expectoration, the frequent moist râles at the left base and the beneficial effects of bronchoscopic treatment. However, the patient obtained no relief from postural drainage. Lipiodol studies were not made but the larger bronchi showed no dilatation at bronchoscopy. It is possible that such studies might have been useful in explaining the true mechanism of the cough, by demonstrating the alteration in size and calibre of the left main bronchus and its relation to the heart shadow.

The most serious complication of the rheumatic disease in this patient was the formation of a large pedunculated mural thrombus in the dilated left auricle. This proved to be the actual cause of her death. It has been shown by Graef, Beiger, Bunim and de la Chapelle⁷ that such antemortem thrombi are fairly common in the left auricle and appendage of a patient with severe mitral stenosis, congestive failure, auricular fibrillation and rheumatic inflammation of the

auricular muscle. All these conditions were fulfilled by our patient whose heart irregularity was already present for an unknown period of time when she was first seen six years ago, and who showed at autopsy a slit-like mitral orifice and outstanding auricular endocardial changes. The possible relation of the mural thrombus in this case to the patient's cough is a matter of speculation. At autopsy the attachment of the thrombus was found to be in the upper portion of the left auricle and it was of tumor-like hardness. It is not improbable that the effective pressure of the enlarged left auricle upon the overlying bronchus was considerably enhanced by the hard thrombus mass in that region.

The terminal clinical picture was marked by peripheral circulatory collapse rather than by congestive heart failure. Her blood pressure was unobtainable, she was intensely cyanosed, and her limbs were cold and clammy. The autopsy indicated that active rheumatic infection was present at the time of death, which accords with the statement of Graef et al.⁷ that the persistence of active inflammation appears to be the chief factor in the development of auricular thrombi. Furthermore, there were evidences that the thrombus had undergone considerable recent enlargement through propagation upon its surface. Her final collapse was apparently of rather gradual development instead of sudden development as in cases of ball-valve thrombus of the left auricle in which the thrombus lies free within the cavity of the auricle and produces sudden plugging of the mitral orifice. The latter syndrome was recently reviewed by Aionstein and Neuman⁸ who, however, state that the separation of cases of ball thrombus from cases of pedunculated thrombus of the left auricle is of academic interest since the symptoms may be similar. In the present case peripheral circulatory failure was of such marked degree and the volume of blood in circulation so markedly decreased that the lungs appeared practically bloodless at autopsy. Notwithstanding, they showed histological evidences of previous congestion of long duration.

SUMMARY

1 A case is reported in which severe chronic and productive cough was the chief symptom for six years in a woman with mitral stenosis.

2 Auricular enlargement and widening of the tracheobronchial angle to 135° were found at autopsy.

3 The case was complicated by the presence of a large pedunculated thrombus of the left auricle which terminally precipitated circulatory collapse of peripheral type, the latter probably explains the nearly bloodless condition of the lungs and other viscera at autopsy.

The writer wishes to express appreciation to Dr. Sylvan E. Moolten for the autopsy material and for his kind advice and suggestions.

REFERENCES

- 1 KING, F., HITZIG, W. M., and FISHBERG, A. Recurrent laryngeal paralysis in left ventricular failure, *Am. Jr. Med. Sci.*, 1934, **clxxviii**, 691.
- 2 NICHOLS, C. F., and OSTRUM, H. W. Unusual dilatation of the left auricle, *Am. Heart Jr.*, 1932, **viii**, 205.
- 3 STEELE, J. MURRAY, JR. Compression and displacement of the bronchi in mitral stenosis, *Am. Heart Jr.*, 1928, **iv**, 53.

- 4 ROUTIER, D, and DE BALSAC, R H Tracheal and bronchial modifications during the course of certain cardiopathies affecting the pulmonary artery, *Brit Jr Radiol*, 1929, xi, 150
- 5 ROUTIER, D, and DE BALSAC, R H Modification of the trachea and the bronchi in mitral disease, *Arch d mal du coeur*, 1937, xxx, 861 (Abstr *Am Heart Jr*, 1939, xvii, 257)
- 6 GRAYBIEL, A Progress in internal medicine Diseases of the heart, *Arch Int Med*, 1940, lxxv, 1053
- 7 GRAEF, I, BERGER, A, BUNIM, J, and DE LA CHAPELLE, C Auricular thrombus in rheumatic heart disease, *Arch Path*, 1937, xxiv, 344
- 8 ARONSTEIN, E C, and NEUMAN, F Ball thrombus of the heart, *Arch Path*, 1939, xxvii, 907
- 9 BLOOMFIELD, A L Dysphagia with disorders of the heart and great vessels, *Am Jr Med Sci*, 1940, cc, 289

ASSOCIATION OF POSTURAL HYPOTENSION WITH SYMPATHETIC NERVOUS SYSTEM DYSFUNCTION; CASE REPORT, WITH REVIEW OF NEUROLOGIC FEATURES ASSOCIATED WITH POSTURAL HYPOTENSION *

By RICHARD H YOUNG, M D, F A C P, *Omaha, Nebraska*

THE term orthostatic, or postural, hypotension has been applied to a condition characterized by a marked fall in the systolic and diastolic blood pressures when the patient changes from the recumbent to an erect posture. The salient features, besides the orthostatic hypotension, in order of frequency, are 1 Weakness, 2 Anhidrosis, or hypohidrosis, 3 Increased distress in summer, 4 Greater urinary frequency at night, 5 Variation in pulse rate with change in posture, 6 Loss of libido and potentia, 7 Orthostatic syncope with loss of consciousness, 8 Low basal metabolic rate, — 10 or lower, 9 Blood urea of 40 or more mg per 100 cc, 10 Pallor, 11. Secondary anemia, 12 False appearance of youth, 13 Neurologic signs

This disorder was first described in 1925 by Bradbury and Eggleston,¹ and the literature, when reviewed in 1936 by Chew, Allen and Barker,² revealed a total of 26 accepted cases. Although the number of cases is few, 13 cases have been reported from the Mayo Clinic.² It is probable that many cases are overlooked and that many are not reported.

The chief interest in this condition in the past has been in the cardiovascular manifestations. The neurologic features were commented upon by Chew, Allen and Barker,² who found neurologic signs in 23 per cent of the cases. This did not include the case reported by Alvarez and Roth³ in which an undiagnosed illness, with features of a mild encephalitis preceded the onset of the orthostatic hypotension. In the five cases with neurologic signs there were no constant findings.

Case 3 in the report by Bradbury and Eggleston¹ had inequality of the pupils, hyperactive tendon reflexes and a bilateral Babinski sign.

* Received for publication October 14, 1940

Ganshorn and Horton ⁴ reported a patient who had slight ptosis of the upper right eyelid, inequality of the pupils, questionable enophthalmos, slight horizontal nystagmus and some difficulty in articulation. There was slight tremor of the right arm on movement, the abdominal reflexes were absent, the patellar reflex and ankle clonus were increased, the Babinski sign was questionably present, and there was diminished sensibility to the tuning-fork. The gait was somewhat ataxic, and fairly definite positive results were obtained with Romberg's test.

Croll, Duthie and MacWilliam ⁵ reported a patient with an Argyll Robertson pupil on the left side and with absent patellar reflexes.

In case 5, reported by Chew, Allen and Barker,² there was definite evidence of syphilis of the central nervous system. There were Argyll Robertson pupils, a right VI nerve paralysis, loss of patellar and Achilles reflexes, diminution of vibratory sense in the lower extremities and a positive Romberg sign. In case 6 of the same series, the patient had unequal pupils, and the larger pupil would not dilate further when cocaine hydrochloride was instilled in the conjunctival sac. In addition, there was hypoactivity of the anal sphincter. These authors quote Woltman as suggesting that the changes in the central nervous system, occasionally seen in cases of orthostatic hypotension, may be the result of irreversible chemical changes which are caused by deprivation of oxygen that is in turn brought about by the drop in blood pressure during orthostatism.

Ellis and Haynes,⁶ in an article on postural hypotension with particular reference to its occurrence in diseases of the central nervous system, report six cases in four of which there were definite evidences of neurologic disease, and an additional case in which there was some evidence of involvement of the central nervous system. They accept the belief that postural hypotension results from a failure of the normal sympathetic vasomotor reflex to produce vasoconstriction when the subject assumes an erect position. Because of the widespread effect, it was their belief that the site of the lesion is either in a sympathetic center, or in an efferent pathway controlling the entire response, or it is generalized throughout the efferent pathways or nerve endings.

Bickel and Demole ⁷ have reported a case and have stressed the importance of disease of the central sympathetic centers and pathways in the etiology of the condition.

Interest in the neurologic features of this disorder was aroused by the case to be reported, which showed neurologic changes, and by study of the neurologic features in the previously reported cases. Further stimulation was provided by the report of Ransom, Kabat and Magoun ⁸ on the autonomic responses to electrical stimulation of the hypothalamus, preoptic region and septum. In certain indefinite regions, it was possible by electrical stimulation to obtain a marked fall in blood pressure and changes in bladder contractility.

CASE REPORT

S. A. J., a 43-year-old minister, was referred to Dr. G. A. Young for examination August 26, 1936, by Dr. H. S. Andrews, of Minden, Nebraska.

The chief complaints were persistent dizziness, weakness in the legs and difficulty in walking, aching pains in the body, and difficulty in urination.

The patient had been perfectly well until about five years previously. At that time he first began to notice difficulty in urination, associated with increased frequency

and some dribbling. A physician had first been consulted three years previously because of burning on urination. This persisted over a period of time, and on January 14, 1935, the bladder difficulty was thoroughly investigated by Dr. Anton Hyden of Sioux Falls, South Dakota. Cystoscopic examination revealed about four ounces of residual urine. The mucosa of the bladder was very much inflamed. Observation of each ureteral meatus showed the urine coming out in slow rhythmic spurts. There was no real obstruction found. The urine from the ureteral catheterization was initially clear, but the bladder urine was found to be filled with pus cells and a great number of colon bacilli. The pyelogram showed only some haziness in the middle calyces of the right kidney pelvis. A cystogram and aurogram showed the bladder to be slightly contracted, although on filling it would hold a good amount of fluid. The roentgen-rays showed some reflux into the ureters. The diagnosis was cystitis due to the colon bacillus and some involvement of the nervous system causing a lack of tone of the sphincteric muscles. The cystitis disappeared on treatment with a ketogenic diet. On August 8, 1935, a prostatic resection was done by Dr. Hyden because of protrusion of the lateral lobes of the prostate, in an effort to relieve a possible obstruction, and in the hope that this might provide a greater ease in emptying of the bladder.

For a period of two and one half years prior to examination there had been dizziness on sudden change of position or with exertion. Frequently during that time there were what were described as "nerve aches" in the extremities, particularly during the morning. In addition, there were complaints of tremor of the hands, a lack of sexual desire, an inability to obtain an erection or orgasm.

During the three months before being seen, the patient complained particularly of an unsteadiness in gait and marked weakness of the legs. It was necessary for him to walk slowly to keep from staggering. Dizziness became almost constant, and during the mornings there had been considerable blurring of vision.

Past history revealed that there had been a normal birth and early development. The only serious illnesses were scarlet fever at the age of 10 years, an apparently uncomplicated case of influenza in 1918, and attacks of what were described as "inflammatory rheumatism" in 1913 and 1926. The history by systems gave little additional data, except for constipation and a tendency toward early morning awakening. The personal history revealed that he had had a college education, and had been active in his duties as a minister. He was married, and had four children ranging in age from 7 to 16 years. The family history was negative.

Physical Examination The physical examination revealed a well developed and nourished man, 5 feet 9¾ inches in height, weighing 143 pounds. There was a poverty of facial expression and a stooped posture. There was slight increase in moisture of the face. The mouth was edentulous. The nose, throat and respiratory tract were negative. The heart contour was normal, by percussion, and the heart sounds were regular and of good quality. The pulse rate was 90. The blood pressure was 148 mm Hg systolic and 96 mm diastolic in the supine position. Because the referring physician (Dr. Andrews) had found a low blood pressure, the patient was raised to a sitting position, and the blood pressure was found to be 68 mm Hg systolic and 40 mm diastolic. When standing, the patient complained of dizziness, and the blood pressure was found to be 44/20. The abdomen, genitalia and extremities were negative. A rectal examination revealed a marked relaxation of the anal sphincter, the prostate was normal.

Neurologic Examination Cranial Nerves

- I Normal
- II Vision grossly normal. Fields were normal. Ophthalmoscopic examination showed normal discs. The retinal vessels were of normal caliber and distribution. There was no change in the retinal vessels noted with change in position.

- III } The pupils were of good size, equal, round and regular
 IV } The reaction to light was perhaps somewhat sluggish Extraocular move-
 VI } ments were normal
 V } Normal
 VII } Normal
 VIII } Normal
 IX } Voice was husky Examination of the larynx by Dr W A Cassidy
 X } revealed no true paralysis, but a distinct lagging and loss of tone of the
 left vocal cord Each ventricle appeared unusually deep and conspicuous
 XI } Normal
 XII } Normal

Motor Status No focal weakness or atrophy Fine tremor of the extended fingers There was no remarkable change in muscle tone, but there was a definite bradykinesia

Coordination Normal

Reflex Status Deep reflexes were equal and active Superficial reflexes were normal, except for the abdominals which could not be obtained No pathologic forms were present

Sensory Status Normal

Sphincters Rectal sphincter relaxed

Laboratory Findings Urinalysis negative Hemoglobin 83 per cent Red blood cells 4,130,000 White blood cells 6,200 Blood urea nitrogen 31 mg per cent Basal metabolic rate minus 2 per cent

Lumbar Puncture Pressure, 4 mm of Hg Cells 0 Protein normal Wassermann reaction negative Colloidal gold 1123332100

Blood Pressure During the period of hospitalization, there was no essential change in blood pressure until medication was given Before placing the patient on medication, the effect of different drugs was tried

	<i>Prone</i>	<i>Sitting</i>	<i>Standing</i>	
Blood pressure	108/70	84/58	58/40	Pulse 96
0.5 cc of adrenalin (1-1000), given intramuscularly, and blood pressure after				
2 min	188/94			
3 min		258/158		
5 min			154/96 (not dizzy)	
7 min	204/112			
10 min	194/106			
15 min	158/98			
60 min	140/90		64/58 (very dizzy)	

The left hand was immersed in a pan of ice water, and very little change in blood pressure was noted

	<i>Prone</i>	<i>Sitting</i>	<i>Standing</i>
Blood pressure	120/76	80/62	42/36
Ephedrine Sulphate, gr 3/8, was given intramuscularly, and blood pressure after			
1 min	140/96		
3 min	148/110		
5 min	158/106		
10 min	160/116	104/84	50/38

Pilocarpine, gr $\frac{1}{8}$, given with a hot drink by mouth, produced only a moderate amount of perspiration and chiefly over the forehead, to a less extent in the axillae and not noticeably elsewhere

Ergotamine tartrate orally produced no significant changes

Reaction to Mecholin (Acetyl Beta Methylcholine Chloride)

<i>Prone</i>			
Blood pressure	130/86		
Mecholin, 05 gm, given subcutaneously, and			
blood pressure after			
1 min	52/10	Pulseless at wrist	Heart rate 36
3 min	58/32	Pulse—	68
6 min	64/28	Pulse—	64
15 min	68/28	Pulse—	84
30 min	82/54	Pulse—	112
45 min	158/100	Pulse—	112

Immediately after injection, the patient complained of a "dazed" sensation and of difficulty in breathing. The respirations increased to 32 per minute. There was also an immediate desire to void and a partial emptying of the bladder. Within a minute there was a profuse generalized perspiration, a great increase in salivation, and a sharp constricting feeling in the rectum.

Roentgen-Ray Findings Roentgen-ray studies of the skull were normal.

Fluoroscopy of the chest showed the lungs and thorax to be essentially clear. The cardiac shadow was slightly, if at all, enlarged, regular in pulsation, and did not seem to change in size in the upright position during periods of faintness.

Cystoscopic Examination A cystoscopic study was done by Dr P S Adams, and the mucous membrane of the bladder appeared normal throughout. Cystometric studies showed evidence of an atonic, dilated bladder. There were 280 c c of residual urine with the cystometric examination. The first desire to void came after 300 c c had been introduced. The pressure was 0. Pain was experienced after 650 c c with a pressure of 4. Severe pain at 1100 c c, with a pressure of 30. Strain elevated the pressure to 40.

Medication During the hospital stay of 33 days, the patient was tried on benzedrine and ephedrine. Both drugs offered relief, although the benzedrine appeared to cause more discomfort in the way of palpitation and wakefulness. Because of the Parkinsonian features in this case, he was placed on stramonium, and this offered some relief. The best results were obtained with a combination of ephedrine, $\frac{3}{8}$ gr five times a day, and tincture of stramonium, minims 40, three times a day.

COMMENT

A review of the literature revealed few cases that exhibited the striking degree of sympathetic involvement reported in this case. From a neurologic standpoint, the patient presented a clinical picture of a Parkinsonian syndrome of the bradykinetic type. The posture was one of moderate flexion, the skin about the face oily, with a paucity of facial expression. There was no appreciable rigidity, but the movements of the extremities were very slow and apparently difficult to initiate. There was a fine tremor present which was not typical of basal ganglia disease.

The lack of sympathetic tone in this case was evidenced by the severe degree of postural hypotension, the impotency, the relaxed rectal sphincter and the dilated, atonic bladder. The response to drugs showed a marked improvement with adrenalin, and to a less extent with ephedrine. The reaction to acetyl beta methylcholine chloride, 0.5 gm., was particularly striking. The parasympathetic stimulation produced marked embarrassment with sharp decline in blood pressure in the prone position, a heart rate of 36 and inability to obtain the pulse at the wrist. It is of interest that the best results from the standpoint of treatment were obtained by a combination of ephedrine, a sympathetic stimulator, and stamonium, a parasympathetic inhibitor. It was felt that these two drugs exerted a synergistic effect.

Although other cases of postural hypotension fail to show the lack of sympathetic activity to the same degree, they do show, in association with other neurologic signs, some features of sympathetic embarrassment. In the course of the examination of neurologic patients two other cases of postural hypotension to a minor degree have been seen. A case of narcolepsy revealed a decrease in blood pressure from 126 mm Hg systolic and 80 mm diastolic to 112 mm Hg systolic and 85 mm diastolic in changing from the prone to the standing position. At the same time, the pulse rate increased from 72 to 100 per minute. A second case was a 59 year old farmer who complained of dizziness and faint spells associated with light-headedness. In addition he had experienced difficulty in walking, especially at night, for two to three years previously. Blood pressure in the prone position was 110 mm Hg systolic and 70 mm diastolic, with a pulse rate of 72. On standing, the blood pressure dropped to 82 mm Hg systolic and 65 mm diastolic, and the pulse rate increased to 88. This patient had a diminution in vibratory sense in the lower extremities as the only neurological finding, and this was associated with an absence of free hydrochloric acid. Blood count, however, was normal. The neurologic features of this case were those of an early subacute combined sclerosis and associated postural hypotension. These findings are similar to those seen in the tabetic cases reported by Ellis and Haynes.⁶

It is doubtful that all cases of postural hypotension have the same etiology. It has been suggested that in some cases the carotid sinus may play a rôle, and others have suggested the possibility of a disturbance of the endocrine glands, toxic agents or trauma. In the case extensively reported in this paper, it is felt that the etiologic factor is a disorder of the nervous system, probably in the hypothalamic region, exerting depressing effect on the function of the sympathetic nervous system.

In view of the frequency of neurologic findings in cases of postural hypotension, a careful investigation of the neural status of each patient would seem to be indicated in an effort to determine the etiologic factor.

SUMMARY AND CONCLUSIONS

A review of the literature reveals that neurologic features are quite common in cases of postural hypotension. In recent years there has been an increasing interest in the possibility that postural hypotension is a manifestation of dysfunction of the sympathetic nervous system.

A case is reported which shows clinical features of a bradykinetic type of Parkinsonian syndrome associated with marked postural hypotension and other manifestations of sympathetic nervous system dysfunction

As a result of pharmacological experience in this case, it is suggested that the best method of therapy is one which produces sympathetic stimulation with ephedrine or benzedrine, and parasympathetic inhibition by drugs of the atropine group

BIBLIOGRAPHY

- 1 BRADBURY, S, and EGGLESTON, C Postural hypotension a report of three cases, *Am Heart Jr*, 1925, 1, 73
- 2 CHEW, E M, ALLEN, E V, and BARKER, N W Orthostatic hypotension, *Northwest Med*, 1936, xxxv, 297
- 3 ALVAREZ, W C, and ROTH, G Orthostatic hypotension, *Proc Staff Meet, Mayo Clin*, 1935, x, 483
- 4 GANSHORN, J A, and HORTON, B T Postural hypotension a report of a case, *Proc Staff Meet, Mayo Clin*, 1934, ix, 541
- 5 CROLL, W F, DUTHIE, R J, and MACWILLIAM, J A Postural hypotension report of a case, *Lancet*, 1935, 1, 194
- 6 ELLIS, L B, and HAYNES, F W Postural hypotension, *Arch Int Med*, 1936, lvi, 773
- 7 BICKEL, G, and DEMOLE, M L'Hypotension arterielle arthostatique, *Rev méd de la Suisse Rom*, 1936, lvi, 1
- 8 RANSOM, S W, KABAT, H, and MAGOUN, H W Autonomic responses to electrical stimulation of hypothalamus, preoptic region and septum, *Arch Neurol and Psychiat*, 1935, xxxiii, 467

PRERENAL UREMIA DUE TO PAPILLOMA OF RECTUM¹

By ROBERT W GARIS, M D, *Baltimore, Maryland*

THE term prerenal azotemia was adopted by Fishberg¹ in 1934 to designate that form of blood nitrogen retention not due primarily to renal insufficiency but to factors affecting the circulation or the composition of the blood before it reached the kidneys. The designation prerenal azotemia was deemed preferable to the older and frequently used expression extrarenal azotemia, since the latter failed to differentiate from the common azotemias due to obstruction of the urinary passages. Only in recent years, with the wide-spread development of laboratory medicine, has the commonplace character of prerenal types of nitrogen retention been recognized. Review of the literature, however, failed to reveal any example of high-grade prerenal azotemia due to non-obstructing rectal tumor. For this reason, the following case seemed worthy of mention.

CASE REPORT

A C C was a white male of 40 who was first seen at his home on March 26, 1939, at which time he complained of malaise and exhaustion. Five days previously he had gone to bed with headache, general aching, anorexia, weakness, stuffiness in the head, and feverishness. Three days later he felt worse, having nausea, increasing headache,

* Received for publication July 22, 1940

and exhaustion. He also felt drowsy, but was unable to sleep. The only other feature elicited at that time was the fact that he had been getting up to urinate three or four times a night for several months or more. His past health had been quite good, and there had been no serious illnesses and no operations. The family history was non-contributory.

Physical examination revealed a well-nourished and developed middle-aged man who looked tired, but not acutely ill. There was considerable restlessness. Although he seemed rational, his responses were slow and at times a little uncertain. Respiration was just a bit labored. The complexion was sallow, but the conjunctivae were of good color. Temperature was 98° F, pulse was 80 per minute, and the blood pressure was 136 mm Hg systolic and 96 mm diastolic. The rest of the examination was negative, apart from a slightly enlarged liver. There was no dependent edema.

Examination of a specimen of urine disclosed a one plus albumin, innumerable granular casts, frequent white blood cells, and occasional red blood cells. Some type of nephritis with early uremia was suspected and hospitalization was advised, although not carried out until the following day.

By the time of admission to the Union Memorial Hospital the patient had become more drowsy and restless, and respirations were of the deep Kussmaul type. Emergency blood non-protein nitrogen was 101 mg/100 cc. Urine was scant, with microscopic findings as before, specific gravity of 1.018, and gave a positive test for diacetic acid. The blood picture showed hemoconcentration and was as follows: red blood cells—6,120,000, hemoglobin—124 per cent, white blood cells—15,400, of which 80 per cent were polymorphonuclear cells. Sedimentation rate (corrected) was 12 mm in one hour, volume packed red blood cells (Hematocrit)—59.

Although increased fluids by mouth and vein were begun at once, on the following morning the blood non-protein nitrogen was 120 mg, urea nitrogen 86 mg, creatinine 2.6 mg, sugar 129 mg, and chlorides 264 mg. Several times during the first night it was noticed that the patient appeared to be incontinent of a thin, watery material from the rectum. Rectal examination on the following day revealed a large, soft, sessile, overhanging mass, mostly posterior and easily palpated with the end of the examining finger. No areas of induration could be felt, although the mass bled easily and a colorless, thin, watery, mucoid secretion without fecal odor was expelled on removing the finger. Questioning revealed that it was to pass small quantities of this material that the patient had been getting up several times each night, urination being merely coincidental to these passages. Apparently, occasional similar passages had been occurring during the daytime in addition to a more formed stool daily.

Sigmoidoscopic examination by Dr. Harvey Stone confirmed the digital examination, and showed the mass to extend well up into the sigmoid colon beyond the reach of the instrument, although it could not be inserted full-length due to the poor cooperation of the patient. Again, 50 or 60 cc of the same non-fecal secretion were expelled through the sigmoidoscope. In view of the extremely low blood chlorides without a history of vomiting, it was decided to study the chloride content of this secretion. Qualitative test was strongly positive and quantitative analysis revealed 687 mg of chloride per 100 cc. This finding helped to clarify the clinical picture, it being assumed that the uremic-like syndrome, dehydration, and probable acidosis were due to the continued loss of electrolytes and fluid by way of the secretion from this massive tumor.

Therapy was first directed toward sufficient replacement of salt and fluids in the system to restore the normal electrolytic pattern and to supply the kidneys with water to carry off the excess nitrogenous wastes. Fluids and salt tablets by mouth, sub-pectoral infusions of normal saline, intravenous glucose and saline, and eventually a continuous intravenous cannula in the foot with alternating saline and glucose were all employed. During the first 24 hours in the hospital the clinical picture had pro-

gressed to the point of a toxic delirium and irrational state, with incontinence of the bowel and toxic paresis of the bladder, the latter necessitating catheterization several times daily. By this time, however, the kidneys had begun to function, and during the next four days the blood non-protein nitrogen dropped progressively to 92, 60, 36, and 26 mg /100 c c, with corresponding increase in blood chlorides to 313, 346, 412,



FIG 1 Gross specimen of excised papilloma of the rectum

and 644 mg per cent respectively. Clinical improvement was even more striking, and the patient stated that he felt better than he had in months. The urine likewise gradually cleared, examination on the eleventh day after admission showing no albumin and only a rare white blood cell microscopically. Fifteen-minute phenolsulphonphthalein test at this time showed a dye excretion of 23 per cent, and a Fishberg concentration test revealed a maximum specific gravity of 1.022. Blood picture on the ninth hospital day was normal: hemoglobin 90 per cent, red blood cells 4,800,000, and white blood cells 6,700, with a normal differential count. Further studies of the

rectal secretion showed a chloride content of 726 mg/100 cc with total proteins of 10 gm per cent, of which 0.4 gm was albumin and 0.6 gm globulin. Serum proteins were 5.8 gm, albumin 4.1 gm, globulin 1.7 gm, and A/G Ratio 2.4. Blood calcium was 9.0 mg and blood phosphorus was 4.4 mg/100 cc.

Roentgen-ray visualization of the kidneys disclosed them to be normal in size, shape and position with no evidence of urinary calculi. Barium enema revealed a large tumor mass, approximately six inches in length, extending from the lower sigmoid to the lower portion of the rectum.

On the sixteenth hospital day, the patient having continued well and having maintained normal blood non-protein nitrogen and chlorides, an abdomino-perineal resection of the rectal tumor was performed by Dr. Stone under cyclopropane anesthesia.

An unusually dilated, long Meckel's diverticulum was initially removed, following which the pelvic peritoneum was incised and the sigmoid freed as much as possible from its mesentery without too much interference with the blood supply. The sigmoid



FIG 2 Section from papilloma of the rectum

was then pushed down into the hollow of the sacrum and the pelvic peritoneum closed anteriorly. After routine abdominal closure, the patient was placed in the dorso-lithotomy position and a perineal incision was made. The rectum, including the tumor and an inch of normal bowel on each end, was removed in toto, the external anal sphincter being preserved and the sigmoid being pulled down and sutured to the sphincter and surrounding structures. The patient left the operating room in good condition, 500 cc of citrated blood being given him during the latter part of the operation.

On gross pathological examination of the rectal specimen (figure 1), the tumor mass appeared approximately oval and measured 7" long \times 5" wide \times 1½" thick. The villous, cauliflower-like growth had a uniform, soft consistency and was confined to the mucosa. Microscopic sections (figure 2) showed an extremely thick mucosa formed by bundles and coils of well-formed tubules side by side, with very little interstitial stroma. The cells were uniform in morphology and columnar in shape, with only occasional mitotic nuclei. There were many normal-appearing goblet cells. There was no invasion beyond the submucosa, although in several areas the tortuosity of the tubules and the buckling of the epithelial layers suggested a transitional stage which could be interpreted as early carcinoma. No lymphatic involvement was observed.

For the first week following operation the patient did fairly well, although obstinate distention accompanied by occasional vomiting and rather severe abdominal pain persisted in spite of continuous nasal-tube decompression, pitressin, and other customary measures. He began to have natural fluid bowel movements on the sixth postoperative day without, however, much relief of the distention and pain. Intravenous and subcutaneous fluids were maintained daily.

On the eleventh postoperative day the patient vomited 50 c c of bloody fluid, followed by a sharp drop in blood pressure and a state of surgical shock. Hematemesis of both bright red and dark blood of amounts varying from a few to several hundred cubic centimeters continued at frequent intervals until death ensued less than 72 hours later, on April 23. Both large and small transfusions of citrated blood, ample morphia sedation, intramuscular hemostatic material, and measures to combat shock were all unavailing. A few hours before death dark red blood was also passed per rectum.

Necropsy was performed by Dr. Walter C. Merkel. The following abstracts are from the report of the examination. Upon opening the abdomen, the intestines were found to be enormously distended and of a reddish-blue color. Many of the loops of intestines were stuck together by fibrinous adhesions. Slight pressure on the bowel revealed a perforation at the operative site where the diverticulum had been excised. There was a separation at one end of the suture line, with reinforcement on the serosa by an adjacent loop of ileum. The floor of the pelvis was intact, and the suture lines secure and actually healed. There was no exudate, and no evidence of metastasis.

Along the greater curvature of the stomach, in direct line of the esophagus, were many punched-out erosions, which averaged $\frac{1}{2}$ to 2 cm in diameter. Some of these ulcers extended down to the peritoneum. They were without inflammatory reaction and suggested to the pathologist a traumatic effect from the esophageal tube. The other pertinent findings were cloudy swelling of the liver and kidneys, acute splenic tumor, terminal right pleural effusion, and hemoperitoneum (thought to be post-mortem due to manipulation of the intestinal tract). The kidneys definitely showed no signs of acute or chronic nephritis.

COMMENT

In the subject of this case report, there had been an excessive fluid and electrolyte loss from the bowel for at least several months, although the frequent small liquid passages were considered neither by the patient nor by the medical observers to be synonymous with a diarrhea. It appeared as if there occurred a collection of fluid material in the recto-sigmoidal region which stimulated a desire for passage when the amount reached a certain quantity. The passages were all small, at rather regular frequent intervals, and apparently in addition to a daily more formed stool. Sigmoidoscopic examination tended to confirm this impression, since the material extruded was a chloride-rich, thin, colorless, mucoid fluid without notable odor. It was considered by all observers to be a secretion from the large rectal mass (normal rectal mucosa cannot secrete salt) rather than a diarrheal stool from higher up in the intestinal tract. It was definitely established that the chloride content of this fluid was very high and almost double the correspondingly low blood chloride. Presumably, basic electrolyte was also lost in producing the clinical picture mentioned.

In association with the very evident dehydration and the probable acidosis, there was a clinical state simulating uremia. Very high blood non-protein nitrogen, albuminuria, and innumerable granular casts in the urine were accompanied by restlessness, headache, hyperpnea, irrational stupor, and incontinence of bowel and bladder. The extremely rapid disappearance of this clinical picture follow-

ing the parenteral administration of large quantities of water, salt and glucose, together with the equally rapid return of normal renal function and urinary findings, practically excluded all types of nephritis and primary kidney disease (a conclusion verified by autopsy). Consequently, this case was classified as an instance of prerenal uremia due to fluid and electrolyte loss per rectum, apparently by secretion from an essentially benign, non-obstructing, large rectal papilloma.

Brief mention should be made of the type of rectal tumor causing such a profound general disturbance. According to Rankin, Beigen, and Buie,² papilloma or villous tumor of the rectum is one of the rarest of benign intestinal tumors. Apparently originating from the intestinal mucosa in the crypts of Lieberkuhn, these tumors are usually sessile, vary considerably in size, have no tendency to invade the deeper structures, and microscopically show single or multiple layers of cylindrical cells supported by delicate vascular stroma. Bleeding, tenesmus, and frequent passages of large quantities of mucus are said to be common symptoms, although there is no characteristic syndrome. Although, both anatomically and clinically, villous papillomata have the nature of benign growths, approximately 20 per cent of all reported cases either were malignant when first observed or else became malignant subsequently. Since there is also a tendency to recur, radical extirpation is the operation of choice.

Finally, the immediate cause of death in the case reported is an unusual one and warrants notice. The patient died of gastric hemorrhages originating in a series of acute ulcers situated on the greater curvature in the direct line of the esophagus. This location and the absence of inflammatory reaction suggest mechanical erosions related in some way to the suction tube, although low tissue resistance due to the profound illness just preceding the operation may have been a contributing factor. It seems more likely that each of these erosions may have begun as a "fox-bite" type of lesion at the point of mucosal contact with an orifice in the nasal tube as a result of strong suction, rather than being due to the mere mechanical pressure or friction of the soft tube against the mucosa.

DISCUSSION OF PRERENAL AZOTEMIA

Blood nitrogen retention in the absence of kidney disease was recognized as long ago as 1832 when O'Shaughnessy³ pointed to a rise of blood urea in cholera. However, modern interest in prerenal types of azotemia was first stimulated in 1914 by Tileston and Comfort,⁴ who found pronounced elevations of blood non-protein nitrogen and urea in three cases of intestinal obstruction. In one patient who died, the blood non-protein nitrogen was 169 on the day before death and the clinical picture was described as strongly suggestive of uremia. Increased absorption of protein nitrogen from the intestine, concentration of blood through fluid loss by vomiting, profound shock, and possible intestinal toxin effect on renal function were suggested as etiological factors in the azotemia.

In 1923, Brown, Eusterman, Hartman, and Rowntree⁵ called attention to the clinical picture of "duodenal toxemia," and ascribed it to a toxic nephritis, the renal injury being evidenced by degenerative lesions in the tubules and diminished phenolsulphonphthalein excretion. In 11 such cases of pyloric and duodenal obstruction, there ensued a state of intoxication simulating uremia, which was characterized clinically by nervous irritability, headache, flushed face, and dehydration, with incoherence, semi-consciousness, and tetany in extreme cases. Uri-

analysis disclosed albumin, casts, red blood cells, and white blood cells, while blood examination revealed an increase in the urea and non-protein nitrogen content, lowering of plasma chlorides, increase in CO_2 combining power, and hemoconcentration. It is now known that complete obstruction of the alimentary canal at any point from the esophagus to the rectum will cause the concentration of non-protein nitrogen in the blood to rise, although it usually requires an obstruction at or above the duodenum to produce symptoms of uremic intoxication.

Similar findings have been described by various groups of investigators⁶ working with experimental duodenal obstruction in dogs, the syndrome terminating in death within a few days unless prevented by parenteral salt solution.

The occurrence of prerenal azotemia in other digestive tract diseases may be briefly reviewed at this point. In addition to high intestinal obstruction, the condition which first stimulated interest in the non-renal types of nitrogen retention, azotemia of varying degrees may also follow the electrolyte and fluid loss from severe diarrhea,^{3,7} and more rarely from fistulae of duodenal, pancreatic, or jejunal origin.⁸ However, simple elevation of the blood non-protein nitrogen rather than frank uremia appears to result from the dehydration, the electrolyte loss, the interference with protein absorption, and the increased destruction of nitrogen material in diarrheal diseases. The chloride loss in normal feces is insignificant, but the liquid stools excreted in diarrhea may contain large amounts of chloride, equivalent to as much as 15 gm of sodium chloride per liter.⁹ Likewise, there is an enormous rise in the output of sodium and potassium in extreme diarrhea.⁹ Such loss may be sufficient to exceed the intake and, with the additional loss in the urine, cause a drain on the alkali stores of the body with accompanying dehydration.

There is more base than acid in all types of feces, so that severe diarrhea causes a withdrawal from the body fluids, and hence from the serum, of more base than acid radicles. Therefore, in addition to dehydration, some degree of acidosis (alkali deficit) usually occurs in pronounced diarrhea, unless there is vomiting, in which case the additional loss of chloride serves to equalize the acid-base deficit. In general, however, this type of azotemia is much more common in infants than in adults, apart from cholera in adults.

In the past few years, numerous reports have appeared concerning the association of marked azotemia with massive gastrointestinal hemorrhages.¹⁰ The elevating effect of blood loss from any source on the level of the blood non-protein nitrogen had been studied many years ago by Taylor and Lewis,¹¹ and later by Buell.¹²

Other conditions related to the digestive tract which are on record as being accompanied by notable azotemia of extrarenal origin are various types of liver damage (especially the so-called "liver death" syndrome), acute pancreatitis and protracted vomiting from whatever cause (hyperemesis gravidarum, peritonitis, and postoperative vomiting).

To these are being constantly added many diseases unrelated to gastrointestinal pathology, such as traumatic and surgical shock, extensive burns, coronary thrombosis, congestive heart failure, reactions from intravenous transfusions and injections, diabetic coma, circulatory collapse of pneumonia and other infections, Addison's disease, heat cramps, serum disease, urticaria, and certain drug intoxications.

The clinical picture of prerenal azotemia^{13, 14} is of necessity superimposed upon each of the widely diverse diseases mentioned above, although there are certain features common to all and certain characteristics differentiating the condition from azotemia due to organic kidney disease. As in patients with Bright's disease, azotemia may exist without clinical symptoms or be accompanied by fatigue and drowsiness, progressing into coma and associated with all of the classical features of uremia. In one of his latest papers,¹⁴ Fishberg makes no differentiation between the character of the uremia of renal disease and that of prerenal azotemia, in that both exhibit a state of dehydration, demineralization, and retention of toxic waste products, and in that both have the same symptom-complex. Harrison and Morton¹⁵ likewise state that the syndrome of prerenal azotemia simulates true uremia in both its chemical and clinical aspects. However, it is true that many of the late manifestations of chronic uremia, such as arterial hypertension, retinal changes, and uremic colitis and pericarditis, are uncommon in prerenal uremia, due to the acuteness and short duration of most of the causative mechanisms. In addition to the symptoms and signs of uremia, a variable degree of peripheral circulatory failure, manifested especially by collapsed peripheral veins with low venous pressure, will usually be detected if sought for carefully.

Laboratory studies are of essential importance in the diagnosis and management of prerenal uremia. The elevated blood non-protein nitrogen is due not only to a rise in urea, but also involves other fractions such as creatinine and uric acid. A marked rise in amino-acid nitrogen is of frequent occurrence in cases of advanced liver damage. Decrease in the blood chloride level is generally present, although there are exceptions. Corresponding reduction in the blood sodium is much more common than is realized, chiefly because this determination is not made routinely. There is recent evidence to indicate that, of the two, hyponatremia is more certain to produce dehydration and azotemia than hypochloremia, since the former leads to a diminished blood plasma volume irrespective of the fluid intake or loss. The acid-base equilibrium of the body, as indicated by the carbon dioxide combining power, may shift toward alkalosis or acidosis depending upon whether the chloride loss or the sodium loss is the greater. Hemoconcentration, as exhibited by increases in the total protein, erythrocyte count, hemoglobin and hematocrit value, is customarily found, and is useful in evaluating the degree of dehydration.

The important urinary features are (1) oliguria or anuria, (2) relatively high specific gravity which, however, may progressively decrease, and (3) the frequent appearance of albumin in small amounts, red blood cells and casts.

The striking clinical improvement and the rapid disappearance of the azotemia under intravenous saline and glucose administration present the final proof of the diagnosis. Such is the treatment indicated in the vast majority of cases of the prerenal syndrome.

The most problematic phase in the consideration of prerenal azotemia is its pathogenesis. Many theories have been advanced since the first recognition of this symptom-complex. Originally, diminished renal function¹⁷ due to degenerative changes in the tubules, so-called "toxic nephritis," was thought to be the chief cause of the azotemia.⁵ Then, with the demonstration of the life-saving qualities of fluid and salt^{6, 8} and the rarity of demonstrable renal pathology in these cases, the condition was considered to be the direct result of dehydration.

and electrolyte loss (particularly chlorides),¹⁸ exaggerated in certain instances by increased destruction of protein and low arterial pressure. In pursuance of this concept, the term hypochloremic azotemia has been recently applied by numerous writers in a wide variety of conditions exhibiting azotemia of prerenal origin. In a comprehensive survey of the whole subject of extra-renal azotemia, Jeghers and Bakst¹⁸ list six basic mechanisms, various combinations of which they believe will explain all of the many situations in which this syndrome arises. These interdependent and interrelated mechanisms are (1) fall in blood pressure, (2) hypochloremia and hyponatremia, (3) dehydration, (4) increased protein catabolism, (5) loss of deaminizing power of the liver, and (6) local renal factors, including cases with tubular damage or edema of the kidney.

It remained for Fishberg¹⁴ to give an unusually concise and well-formulated opinion as to the basic mechanism of prerenal azotemia. Briefly, he first defines the fundamental criterion of impairment of renal function as "a concentration of urine disproportionately low in comparison to urinary volume." He then considers the problem as to whether the azotemia is due to overloading of the kidneys (increased destruction of protein) or to failure of the kidneys, and concludes that the latter can be demonstrated as the cause if kidney function is judged in the light of the above definition. Besides citing previous evidence of impairment of renal function shown by urea clearance and other tests, Fishberg notes that in the vast majority of patients with prerenal azotemia, comparison of the specific gravity with the urinary volume shows a definite decrease in the concentrating ability. Thus, while a specific gravity of 1.020 is evidence of good kidney function when the urinary volume is normal, it is too low if the urinary volume is very small.

The mechanism of impairment of renal function is next discussed. It is shown that hypochloremia, low arterial pressure, toxic nephritis, and alkalosis cannot produce such impairment of themselves and that where present they appear to play accessory rôles at most. A strong array of evidence is finally presented to indicate that the primary pathogenetic factor in most, if not all, instances of prerenal azotemia is decrease in blood flow through the kidneys, mediated by peripheral circulatory failure with decrease in circulating blood volume. In this concept, the decreased urinary volume is ascribed to the diminished volume of blood flow through the glomeruli, and the lessened concentrating ability to impaired tubular function on an ischemic basis, with the intensity of the regressive changes in the tubular epithelium paralleling the degree of diminution in the renal blood flow.

The therapy of prerenal azotemia can be summed up in a few words. In addition to adequate treatment of the underlying disease process, the prime consideration is the restoration of the normal blood volume and electrolytic concentration. In almost all cases, this is best accomplished by the intravenous administration of sodium chloride solution with or without glucose. Peroral administration of fluid cannot be relied upon, and especially in the presence of vomiting, may be positively contraindicated. Relatively moderate amounts of glucose solution, given intravenously, may be sufficient to lessen protein destruction and to combat starvation acidosis, but large quantities of intravenous saline solutions are usually required. The total of both substances must be sufficient to restore the depleted fluid and electrolyte concentration in the body. This will automatically establish a normal urine output with rapid disappearance of the re-

tained nitrogen and other toxic products of catabolism. Furthermore, the kidneys, under fair working conditions, are sufficiently flexible in function to be capable of selective excretion of electrolytes of which there is an excess, and retention of those of which there is a deficiency. This obviates the need for separate administration of bicarbonate, lactate, or other special electrolytic solutions.

Blood and plasma transfusion are particularly indicated in the types of prerenal azotemia associated with shock, notably hemorrhage and trauma. There are other useful measures adaptable to specific cases, but these are of secondary importance and will not be discussed here.

SUMMARY

1 An essentially benign, non-obstructing tumor of the rectum is added to the growing list of gastrointestinal and other miscellaneous conditions which have been observed to cause prerenal azotemia. The chief characteristics which helped to distinguish this instance of prerenal azotemia from the uremia secondary to organic renal disease were the absence of notable impairment of kidney function (especially high specific gravity), the laboratory evidence of marked dehydration (high hematocrit value, etc.) and of electrolyte deficiency, the discovery of the source of these losses from the body, and the quick reversibility of both subjective and objective findings upon fluid and salt restoration. Certain features in the clinical picture, such as normal fundi and normal blood pressure, were also of value in the differentiation. Autopsy verified the prerenal nature of these changes, for the kidneys showed no evidence of pathology apart from cloudy swelling. The mechanism in this case appeared to be one of progressive dehydration and electrolyte loss from the excessive secretion of the neoplasm, followed by sufficient oliguria to induce a clinical picture of acute uremia.

2 The whole subject of prerenal azotemia is briefly reviewed from the historical, clinical, pathogenetic, and therapeutic standpoints. The recent explanation of the pathogenesis by Fishberg appears to be the most logical, and at the same time, the most readily adaptable to all of the variegated types of prerenal azotemia. Under this concept, the azotemia is ascribed to impairment of renal function due to diminution in the volume of blood flow through the kidneys, which results in decreased urinary volume and urinary concentration. The diminished renal blood flow is in turn secondary to lessened circulating blood volume, i.e., peripheral circulatory failure.

3 Villous papilloma, a highly secretory type of rectal tumor, was present in this case. Rectal papillomata of the villous class are quite rare, which may help to explain the lack of similar case reports. Doubtless a corresponding prerenal uremia could follow other types of secretory rectal neoplasms, particularly should they be allowed to progress too long before medical attention is sought, as occurred in this case.

4 Massive hemorrhages from traumatic erosion ulcers of the stomach originating from a suction tube for distention appeared to be the immediate postoperative cause of death.

This patient was seen in consultation by Dr. Warfield T. Longcope and Dr. Harvey B. Stone, to whom the author is particularly indebted for suggestions in the management of this case. The author also wishes to express thanks to Dr. George W. Thorn for his help in the preparation of this report.

BIBLIOGRAPHY

- 1 FISHBERG, A M Hypertension and nephritis, Third Edition, 1934, Lea & Febiger, Philadelphia, p 40
- 2 RANKIN, F W, BARGEN, J A, and BUTE, L A Colon, rectum, and anus, 1932, W. B Saunders & Co, Philadelphia and London, p 405
- 3 O'SHAUGHNESSY, W B (1831-1832): Lond Med Gaz, ix, p 486
- 4 TILESTON, W, and COMFORT, C W Total non-protein nitrogen and the urea of the blood in health and disease, Arch Int Med, 1914, xiv, 620-649
- 5 BROWN, G E, EUSTERMAN, G B, HARTMAN, H R, and ROWNTREE, L G Toxic nephritis in pyloric and duodenal obstruction Renal insufficiency complicating gastric tetany, Arch Int Med, 1923, xxvii, 425
- 6 FELTY, A R, and MURRAY, H A, JR Observations on dogs with experimental pyloric obstruction, Jr Biol Chem, 1923, lvii, 573
HADEN, R L, and ORR, T G Chemical changes in the blood of the dog after pyloric obstruction, Jr Exper Med, 1923, xxxvii, 377
- 7 PETERS, J P, and VAN SLYKE, D D Quantitative clinical chemistry, 1931, Williams & Wilkens Co, Baltimore, Md, p 299 (Cf for list of references)
- 8 WALTERS, W, KILGORE, A M, and BOLLMAN, J L Changes in the blood resulting from duodenal fistula A clinical and experimental study, Jr Am Med Assoc, 1926, lxxxvi, 186
WALTERS, W, and BOLLMAN, J L Toxemia of duodenal fistula, physiologic changes concerned in the production of its characteristic chemical reactions of blood, Jr Am Med Assoc, 1927, lxxxix, 1847
- 9 DRAGSTEDT, L R, MONTGOMERY, M L, MATTHEWS, W B, and ELLIS, J C Fatal effect of total loss of pancreatic juice, Proc Soc Exper Biol and Med, 1930, xxviii, 110
- 10 HARTMANN, A F, and ELMAN, R Loss of gastric and pancreatic secretions and methods for restoration of normal conditions in the body, Jr Exper Med, 1929, l, 387
- 9 HOLT, L E, COURTNEY, A M, and FALES, H L The chemical composition of diarrheal as compared with normal stools in infants, Am Jr Dis Child, 1915, ix, 213
- 10 ALSTED, G Further studies on azotemia following hemorrhage in the digestive tract, Am Jr Med Sci, 1936, cxlii, 198-208
- 11 TAYLOR, A E, and LEWIS, H B A study of protein metabolism under conditions of repeated hemorrhage, Jr Biol Chem, 1915, xii, 71-76
- 12 BUELL, M V Studies of blood regeneration II Effect of hemorrhage on nitrogen metabolism, Jr Biol Chem, 1919, xi, 63-77
- 13 JFGHERS, H, and BAKST, H J Syndrome of extrarenal azotemia, ANN INT MED, 1938, xi, 1861-1899
- 14 FISHBERG, A M Prerenal azotemia and the pathology of renal blood flow, Bull New York Acad Med, 1937, xiii, 710-732
- 15 HARRISON, T R, and MORTON, F M The pathogenesis of the uremic syndrome, Medicine, 1937, xvi, 1-44
- 16 KERFFI-FRONIUS, E Zur Pathogenese der "hypochloremischen" Azotemie, Ztschr f d ges Exper Med, 1936, xcvi, 733-748
- 17 McQUARRIE, I, and WHIPPLE, G H I Renal function influenced by intestinal obstruction, Jr Exper Med, 1919, xxix, 397
- 18 HADEN, R L, and ORR, T G The excretion of nitrogen after upper gastro-intestinal tract obstruction, Jr Exper Med, 1927, xlv, 433

EDITORIAL

THE SIGNIFICANCE OF HUMAN ATYPICAL ISOAGGLUTININS

THE discovery of the human blood groups and their routine determination in the selection of donors for transfusion removed the major peril of this procedure by eliminating most of the serious hemolytic reactions which followed the administration of incompatible blood. In spite of this precaution, however, an occasional reaction of this type has continued to occur. In a large majority of the cases reported in the earlier literature, it could be shown that errors in group determination had been made, and that the blood given had really been incompatible. Improvements in technic and adequate care in performing the tests can eliminate such errors, although they still occur if the tests are entrusted to inexperienced technicians.

In rare instances, reactions have followed the indiscriminate use of universal donors. As a rule, an individual belonging to Group O can serve as a donor for a patient belonging to any of the other groups, since the O cells introduced are not affected by the isoagglutinins which define the major groups. The plasma of O donors does contain agglutinins and probably other substances which can act on the cells of recipients of other groups, but usually this activity is abolished in the blood of the recipient, by dilution or possibly by direct neutralization so that no reaction occurs. In some cases, however, the active substances are present in the O serum in such high concentration that they are probably not adequately neutralized, and a reaction presumably may occur if such blood is given to a recipient of a different group. Such reactions can probably be avoided by measuring the activity of the serum of every prospective universal donor, using only those with a low agglutinin titer.

Apart from reactions of these types, however, serious hemolytic reactions may occur in patients who have received blood from a donor of the same blood group. In most cases this has occurred in patients who have received repeated transfusions, often from the same donor. Although well authenticated cases of this type are rare, a substantial number have now been reported. Among the most carefully studied instances of this type are three cases reported by Wiener and Peters¹. Each received repeated transfusions from donors of the same group. After the earlier transfusions no clinical reaction occurred, although in some instances the expected rise in red cell count and hemoglobin was not obtained. The final transfusion in each case was followed by a severe hemolytic reaction. The usual cross matchings before the transfusions had shown no incompatibility. Blood serum taken from the patients after the last transfusion, however, when tested by a special

¹ WIENER, A. S., and PETERS, H. R. Hemolytic reactions following transfusions of blood of the homologous group, with three cases in which the same agglutnogen was responsible, *ANN INT MED*, 1940, xiii, 2306-2322.

method, agglutinated the donor's cells. There was, therefore, an isoagglutinin concerned, which was different from the major group agglutinins, *a* and *b*.

A study of these sera showed that the agglutinin was identical with one which Landsteiner and Wiener² had demonstrated in rabbits which had received injections of red blood cells of rhesus monkeys. To the corresponding agglutinable factor, present in the monkey cells, they assigned the term *Rh*. A study of many human individuals showed that this same agglutinable factor is present in about 85 per cent of the cases. Landsteiner and Wiener³ have studied the familial incidence of the *Rh* factor. It appears to be inherited as a Mendelian dominant character, independently of the *A*, *B*, *M* and *N* factors.

Except for the phenomenon of panagglutination, a human blood serum has never been found to contain agglutinin active on an agglutinable substance present in its own cells. In the remaining 15 per cent of individuals who lack the *Rh* factor, the injection of cells containing *Rh* may stimulate the production of the corresponding agglutinin. This obviously had occurred in these cases, and was associated with a severe reaction when such blood was reinjected.

It is probable that a similar mechanism constitutes the basis for many, at least, of these intra-group reactions, although in some cases it has been shown that the anomalous agglutinable factor is antigenically different from the *Rh* factor.

The number of *Rh*-negative patients who have received repeated transfusions of *Rh*-positive blood cells must be vastly greater than the number of clinical reactions which have been observed. There must be other factors necessary to bring about the formation of agglutinins and other antibodies in sufficient quantity to cause these reactions.

From the practical standpoint, this adds one more to the precautions necessary to ensure safety in transfusions. At present, reagents are not generally available for identification of the *Rh* factor in human blood, although Landsteiner and Wiener³ have described a relatively simple method of preparing anti-*Rh* serum in guinea pigs. However, it may be possible by means of simple procedures to detect the existence of such incompatibilities. These agglutination reactions are quantitatively much feeble than those which determine the major blood groups, and, unlike them, are usually demonstrable only at low temperatures. If, therefore, the recipient and prospective donor have been shown by the usual tests to belong to the same major group, one may mix serum from the recipient and cells from the donor in a small tube, chill in ice water, centrifugalize, and resuspend the cells.

² LANDSTEINER, K., and WIENER, A. S. An agglutinable factor in human blood recognized by immune sera for rhesus blood, *Proc Soc Exper Biol and Med*, 1940, **XLIII**, 223.

³ LANDSTEINER, K., and WIENER, A. S. Studies on an agglutinin (*Rh*) in human blood reacting with anti-rhesus sera and with human isoantibodies, *Jr Exper Med*, 1941, **LXXVI**, 309-319.

by shaking the tube gently. If clumps are present, the donor presumably is incompatible.¹ The reliability of this procedure, in either a positive or a negative sense, can be determined only by protracted trial. It is certain that reactions do not necessarily occur, even though the recipient's blood contains such agglutinins. Whether or not a negative preliminary test will suffice to exclude such reactions has not yet been demonstrated.

Intra-group reactions have also been described as occurring after a first transfusion, but only in women after labor, or after a still birth. Levine and Polayes⁴ have recently reported such a case in the *ANNALS OF INTERNAL MEDICINE*. In these cases it is believed that the fetus has inherited from the father some agglutinable substance which was not present in the mother. She may then become "immunized" to this fetal factor, with the development of agglutinins, and react immediately if later transfused with blood containing it. The agglutinable factor in this case was not identical with the *Rh* factor of Landsteiner and Wiener. Such cases are relatively rare, and the immunization may depend upon placental defects which permit passage of fetal blood into the maternal circulation.

There is also evidence that such immunization of the mother may result in serious injury to the blood or tissues of the fetus. Levine et al.⁵ have collected a number of cases in which repeated miscarriages or still births had occurred in women whose blood contained such "atypical" agglutinins. In a considerable proportion (seven of eleven) of the cases of erythroblastosis fetalis examined as to this point, the mother's blood contained atypical agglutinin—usually anti-*Rh* agglutinin^{4,5}. In several cases of erythroblastosis they showed that the mother's blood did not contain the *Rh* agglutinable factor, whereas it was present in that of the father and the affected children. Other agglutinable factors probably can cause similar disturbances, however, since in a few instances *Rh* was found in the mother's blood.

In most cases heterospecific pregnancies run a normal course, and the occurrence of erythroblastosis or fetal death presupposes some other contributory or predisposing factors. Further studies along these lines are manifestly needed, not only of these relatively rare congenital anemias, but of unexplained repeated miscarriages and still births.

P W C

NOTICE TO READERS

Because of the unwieldy size of recent volumes of the *ANNALS OF INTERNAL MEDICINE* (approximately 2400 pages), it is planned hereafter to issue two volumes a year. The present volume (Vol XV) will, therefore, terminate with the

⁴ LEVINE, P, and POLAYES, S H. An atypical hemolysin in pregnancy, *ANN INT MED*, 1941, xiv, 1903-1908.

⁵ LEVINE, P, KATZIN, E M, and BURNHAM, L. Immunization in pregnancy. Its possible bearing on the etiology of erythroblastosis fetalis, *Jr Am Med Assoc*, 1941, cxvi, 825-827.

December issue, and the January issue will be Number 1 of Volume XVI. Each volume will have its own index.

Subscriptions will continue to be received on the annual basis.

It is hoped that this change will meet with the approval of our readers and will result in an added convenience in binding the volumes. A number of readers have already obtained binders for the ANNALS OF INTERNAL MEDICINE for the current volume, which, until this announcement, was expected to extend until June, 1942. These official binders have heretofore been manufactured in two books—one for the first six issues of the volume, and one for the second six issues. Those who have obtained the binders for the second six issues of the current volume may return the second binder to the Executive Offices at 4200 Pine Street, Philadelphia, Pa., and have the imprinting thereon corrected without charge, due to the change in the volume designation.

REVIEWS

Gastric and Duodenal Ulcers By HAROLD AVERY, D Sc, M B, M R C P 110 pages, 14 × 22.5 cm John Bale and Staples Ltd, 83-91 Great Titchfield St, London W1 1940 Price, 7/6 d

Because the pathology of uncomplicated peptic ulcer is usually so precise, the novice is apt to conclude that our knowledge of the entire subject is equally definite. Standard texts do little other than foster this view with their customarily didactic approach to the condition. The psychological aspect, and even the fundamental principles of dietary and medical therapy, are often buried in a mass of superficial rules and regulations.

The small volume herein reviewed succeeds in avoiding most of these pitfalls. The subject of peptic ulcer is discussed completely, starting with the basic anatomical and physiological features of the stomach and duodenum. Particular attention is given to etiology. The author in this section describes the constitutional type of individual so frequently affected with the condition. The chapter on treatment is quite complete, and there has been included a series of diets to be used during the different phases of the disease.

For a somewhat brief, but sound discussion of the subject of peptic ulcer this volume is recommended. It should be of considerable value to medical students and general practitioners.

F G D

Obstetrics Oxford Medical Outline Series By HERVEY CLOCK WILLIAMSON, M D, F A C S, and GEORGE SCHAEFER, M D 113 pages, 14.5 × 22 cm Oxford University Press, New York 1941 Price, \$2.00

This attractive little book is the outline of obstetrics in the Oxford Medical Outline Series. The authors have accomplished their task of condensing what they consider the more important and practical considerations of obstetrics into an admirable outline. They state that they have purposely omitted historical data, illustrations and theories on debatable subjects. Important, recent advances such as those in chemotherapy and roentgen pelvimetry, however, have been included.

The book is arranged in a clear, easily followed outline form, with a blank page to be used for notes or drawings, opposite each page of text. There are 19 chapters. The bibliography is brief but embraces recent literature.

In the opinion of the reviewer, this book will find its chief usefulness among medical students who will welcome a brief, authoritative, well-organized and readily usable outline for review and reference.

J E S

The Treatment of Diabetes Mellitus 7th Edition By ELLIOTT P JOSLIN, A M, M D, Sc D, HOWARD F ROOT, M D, PRISCILLA WHITE, M D, and ALEXANDER MARBLE, M D 783 pages, 24 × 15.5 cm Lea and Febiger, Philadelphia 1941 Price, \$7.50

This is an outstanding book on diabetes, now appearing in its seventh edition. It has essentially the same authors contributing to this edition as in the sixth but here a larger part than ever has been borne by the associates of Dr Joslin. The wide field of diabetes is here broken up into 30 chapters. This is practically the same division as in preceding editions except that a most interesting chapter on Allergy and Diabetes

has been added. The different chapters are thoroughly revised and rewritten. Approximately 100 pages have been added to the text.

Due note is given to the recent work of Young, Lukens and Best on the relation of the anterior lobe of the pituitary gland and diabetes.

The section on the treatment of diabetic coma (acidosis) should be read by all who are called upon to treat the diabetic. The authors feel that "experience has amply shown that alkalies are needless and if given in quantities necessary for effectiveness in a purely chemical sense, may be actually harmful." The authors are to be congratulated on maintaining their firm stand that the blood sugar be within normal limits and the urine be sugar free in the successfully treated diabetic.

Without question this classic, as in past editions, will remain essential to all who treat diabetic patients. It cannot be too highly recommended.

J S E

Pulmonary Tuberculosis (A Synopsis) By JACOB SEGAL, M.D. 150 pages, 16 × 24 cm. Oxford University Press, New York, N.Y. 1939. Price, \$2.75.

This small book is, as the title states, a synopsis of the fundamentals of pulmonary tuberculosis. The elementary, practical concepts of the pathogenesis, pathology, clinical types and treatment are presented clearly and in an interesting manner. The style is forceful without being dogmatic. There are a number of appropriate roentgen-ray illustrations.

The book is recommended to the medical student as an excellent introduction to the study of pulmonary tuberculosis. It should also be of help to health officers, social service workers and laymen interested in this subject. Unfortunately no references for collateral reading are given.

E T L

COLLEGE NEWS NOTES

GIFTS TO THE COLLEGE LIBRARY

Acknowledgment is made of the receipt of the following reprints of publications by members of the College

Dr John E Ashby (Associate), Dallas, Tex—2 reprints,
Dr Arthur John Atkinson (Associate), Chicago, Ill—17 reprints,
Dr Jacob M Cahan, F A C P, Philadelphia, Pa—2 reprints,
Dr Earle M Chapman, F A C P, Boston, Mass—1 reprint,
Paul Richmond, Jr, F A C P, Captain, (MC), U S Navy—2 reprints,
Dr Leslie M Smith, F A C P, El Paso, Tex—2 reprints,
Dr Edward J Stefaniec (Associate), Lakewood, Ohio—2 reprints,
Dr Alexander S Wiener (Associate), Brooklyn, N Y—17 reprints

Dr Francis M Pottenger, F A C P, a former President and for many years a Regent of the College, founder and Director of the Pottenger Sanatorium, Monrovia, Calif, was honored on the occasion of his 72nd birthday, September 22, by an "Annual Home Coming" of friends and former patients at the Sanatorium. Approximately three hundred and fifty persons, most of them former patients, were present

Dr Robert H Felix (Associate), Passed Assistant Surgeon of the United States Public Health Service, and for the past few years stationed at Lexington, Ky, as Chief of the Medical Service and Researcher in Drug Addiction at the United States Public Health Service Hospital, has been assigned to the Johns Hopkins University School of Hygiene and Public Health for the current academic year, where he will pursue postgraduate work leading to the degree of Master of Public Health

Dr William Harvey Perkins, Professor of Preventive Medicine at Tulane University Medical School, has been named Dean of Jefferson Medical College of Philadelphia. Dr Perkins, who was graduated from Jefferson in the class of 1917, succeeds Dr Henry K Mohler, F A C P, who died on May 16, 1941

The New York Academy of Medicine began its sixteenth series of Friday afternoon lectures on October 31, 1941. All lectures are open to the medical profession and to medical students.

On the program appear the following papers by members of the College

November 14, 1941—"Cancer of the Lung," Dr J Burns Amberson, Jr, F A C P, Professor of Medicine, Columbia University College of Physicians and Surgeons,

January 23, 1942—"Plasma Proteins in Health and Disease," Dr Robert F Loeb, F A C P, Professor of Medicine, Columbia University College of Physicians and Surgeons,

April 10, 1942—"Edema Its Pathogenesis and Treatment," Dr William Goldring, F A C P, Associate Professor of Medicine, New York University College of Medicine

Dr Lyman Bruce Carruthers, F A C P, who is Professor of Medicine and Dean of the Miraj Christian Medical School in Miraj, India, has been appointed Editor of the *Journal of the Christian Medical Association of India, Burma and Ceylon*

Under the Presidency of Dr Aichibald A Barron, F A C P, Charlotte, the North Carolina Neurological and Psychiatric Association held a meeting at State Hospital, Morganton, Friday, October 24, 1941 Dr. Mark A Griffin, F A C P, and Dr William R Griffin, F A C P, both of Asheville, discussed "Electro-Therapy"

Under the General Chairmanship of Dr Walter L Bierring, F A C P, Iowa State Health Commissioner, Des Moines, the Iowa State Department of Health in co-operation with the Iowa State Medical Society sponsored a Special Institute on Industrial Health, September 22-24, 1941 One-day institutes were held in Council Bluffs, Waterloo and Dubuque

Under the Presidency of Dr Hyman I Goldstein (Associate), Camden, the New Jersey Gastro-enterological Society will meet December 1, 1941, in Jersey City The subject of this meeting will be "Surgical Problems in Benign Lesions of the Small Intestine and Malignant Lesions of the Large Bowel" Drs Louis L Perkel, F A C P, Jersey City, Manfred Kraemer, F A C P, Newark, Sigurd W Johnsen, F A C P, Passaic, and Hyman I Goldstein (Associate) will participate in the discussion of the subject

The Woman's Medical College of Pennsylvania held the opening exercises for its 92d Annual Session, September 17, 1941 The College has organized new Departments of Anesthesia, Gastro-enterology and Urology Dr Mary M Spears, F A C P, Professor of Gastro-enterology and Proctology, will head the Department of Gastro-enterology New appointments to the faculty include Dr E J G Beardsley, F A C P, Professor and Head of the Department of Medicine, and Dr Mary H Easby, F A C P, and Dr Clara L Davis (Associate), Clinical Assistant Professors of Medicine

The Mississippi Valley Medical Society held its 7th Annual Meeting in Cedar Rapids, Iowa, October 1-3, 1941 Among the Fellows of the College who participated in the program were

Dr J Vardeman Bell, F A C P, Kansas City, Mo—"Sulfonamide Therapy",
 Dr Delon A Williams, F A C P, Kansas City, Mo—"Gastric Lesions" and
 "Advances in Gastro-enterology",
 Dr LeRoy H Sloan, F A C P, Chicago, Ill—"Clinico-Pathologic Conference",
 Dr Dan G Stine, F A C P, Columbia, Mo—"The Evaluation of Cardiac
 Murmurs",
 Dr O P J Falk, F A C P, St Louis, Mo—"The Prevention of Coronary
 Disease"

The Dallas Southern Clinical Society held the second series of its program of courses for the Continuation of Medical Study in Dallas, October 27-29, 1941 Courses were offered in Cardiology, Diabetes Diagnostic and Medical Gynecology, Traumatic Surgery, Pediatrics—Respiratory Diseases, Dermatology and Syphilology, Roentgenology—Procedures and Interpretation, and Urology Among those who conducted these courses were.

Dr Henry M Winans, F A C P—"Hemodynamics of the Circulation," "Hypoglycemic States and Hyper-insulinism" and "Diagnosis and Treatment of Cardiac Arrhythmias",

Dr W Grady Reddick, F A C P—"Roentgen Aid in the Diagnosis of Heart Disease" and "Insulin Shock and Coma",

Dr William H Potts, Jr, F A C P—"Circulatory Function Tests" and "Pre- and Post-Operative Care of the Diabetic",

Dr Robert M Barton, F A C P—"Principles of Electrocardiography Practical Application of Electrocardiography Tracings and Patients" and "Coronary and Peripheral Vascular Diseases",

Dr Merritt B Whitten (Associate)—"Principles of Electrocardiography Practical Applications of Electrocardiography Tracings and Patients",

Dr David W Carter, Jr, F A C P—"History, Etiology and Incidence of Diabetes Mellitus," "Heart Failure Edema, Dyspnea, Cyanosis" and "The Treatment of Cardiac Failure",

Dr J Shirley Sweeney, F A C P—"Pathological Physiology of Diabetes Mellitus",

Dr T Haynes Harvill (Associate)—"Determination of the Diabetic Diet" and "Computation and Preparation of the Diabetic Diet",

Dr M Hill Metz, F A C P—"The Insulins",

Dr William H Bradford (Associate)—"Congenital Abnormalities of the Respiratory Tract",

Dr H Leslie Moore, F A C P—"The Tonsil and Adenoid Problem",

Dr Everett C Fox, F A C P—"Early Syphilis Diagnosis, Treatment, Drugs, Reactions," "Dermatological Therapeutics," "Demonstration and Discussion of Cases of Common Skin Diseases" and "Demonstration of Bed Patients with Various Types of Skin Diseases, Differential Diagnosis, Treatment, Prognosis and Discussion",

Dr John E Ashby (Associate)—"Congenital Syphilis",

Dr J Bedford Shelmire, F A C P—"Eczema Diagnosis and Treatment," "Demonstration and Discussion of Cases of Common Skin Diseases" and "Dermatitis from Plants",

Dr J Harvey Black, F A C P—"Allergic Diseases of the Respiratory Tract",

Dr John G Young, F A C P—"Tuberculosis in Childhood"

Dr Joseph I Linde, F A C P, New Haven, has been appointed City Health Officer for a six-year term by Governor Hurley of Connecticut

Dr William deB MacNider, F A C P, Kenan Research Professor of Pharmacology of the University of North Carolina School of Medicine, Chapel Hill, recently delivered three lectures on "Acquired Resistance of Tissue Cells," under the auspices of the Department of Materia Medica and Therapeutics of the University of Michigan Medical School, Ann Arbor The subjects of Dr MacNider's lectures were "Repair of Tissue and Tissue Resistance," "The Aging Process and Tissue Resistance" and "The Adjustability of the Life Process to Injurious Agents"

Dr Walter Baumgarten, F A C P, St Louis, has been elected Secretary of the Missouri State Medical Association

The American Roentgen Ray Society held its 42nd Annual Meeting in Cincinnati, Ohio, September 23-26, 1941 Among the speakers were

Dr Tom D Spies, F A C P , Cincinnati, Ohio—"The Manifestations of Vitamin Deficiencies as They Affect the Practice of Roentgenologists",

Dr Byrl R Kirklin, F A C P , Rochester, Minn—"The Meniscus Sign-Complex A Pathognomonic Index of Early Ulcerating Cancer of the Stomach",

Dr Harold J. Stewart, F A C P , New York, N Y—"Contributions of Roentgenology to the Diagnosis of Chronic Constrictive Pericarditis"

Dr Raymond Hussey, F A C P , Baltimore, Md, spoke on "The State Medical Society's Responsibility in Mental Hygiene" and Dr John E Gordon, F A C P , Boston, Mass, spoke on "Epidemiologic Observations in War-Time London," at the 70th Annual Meeting of the American Public Health Association held in Atlantic City, N J, October 11-17, 1941

During September Dr Horton R Casparis, F A C P , Professor of Pediatrics at Vanderbilt University School of Medicine, Nashville, Tenn, gave a series of lectures on pediatrics in Oakland and San Diego, and conducted a course of lectures and clinical discussions before the Southwestern Pediatric Society in Los Angeles, Calif

The Medical Society of Delaware held its 52d Annual Session at Wilmington, October 7-8, 1941 Among the speakers at this meeting were

Dr Harold W Jones, F A C P , Philadelphia, Pa—"Discussion of the Transfusion of Whole Blood, Plasma and Serum",

Dr Lawrence J Rigney, F A C P , Wilmington, Del—"Analysis of the Clinical Data of 47 Proved Cases of Carcinoma of the Pancreas"

A series of extramural courses for physicians was held at Hurley Hospital, Detroit, under the auspices of the Michigan State Medical Society and the University of Michigan Medical School Among those who conducted the courses were

October 1, Dr John M Sheldon (Associate), Ann Arbor—"Office Management of the Allergic Patient";

October 8, Dr Douglas Donald, F A C P , Detroit—"Medical Complications of Pregnancy",

October 15, Dr Richard M McKean, F A C P , Detroit—"Office Management of the Diabetic Patient"

Recently Dr Philip I Nash, F A C P , Brooklyn, N. Y, was honored at a testimonial dinner in recognition of his activities in the Coney Island community Dr Nash has been chairman of the Medical Board of Coney Island Hospital and of the Harbor Hospital for many years, has been President of the Medical Society of the County of Kings and was on the faculty of the Long Island College of Medicine

A course of postgraduate lectures on Geriatrics to be given at Marquette University School of Medicine in November has been announced by the Medical Society of Milwaukee County Among those who will conduct this course are

Dr George Morris Piersol, F A C P , Philadelphia, Pa—"The Problem of Aging from the Internist's Angle",

Dr Hans H Reese, F A C P , Madison, Wis—"The Central Nervous System in the Aged"

The American Academy of Ophthalmology and Otolaryngology held its 46th Annual Meeting in Chicago, Ill, October 19-23, 1941. Dr Burt R Shurly, F A C P, Chairman of the Academy's Preparedness Committee, spoke on "The Rôle of the Academy in National Defense" and Dr Louis H Bauer, F A C P, Hempstead, N Y, spoke on "Aviation Medicine"

Dr Julius Lane Wilson, F A C P, New Orleans, has been appointed President of the Tuberculosis and Public Health Association of Louisiana to fill the unexpired term of Dr William H Perkins, who resigned to become Dean of Jefferson Medical College of Philadelphia

Among the speakers at the annual symposium of Duke University School of Medicine and Duke Hospital on "Problems of Civil and Military Emergencies," held at Durham, N C, October 16-17, 1941, were

Dr Thomas T Mackie, F A C P, New York, N Y—"Problems in Nutrition During Periods of Crisis and Food Shortage";

Dr Alvan L Barach, F A C P, New York, N Y—"Clinical Use of Oxygen",

Dr Russell L Cecil, F A C P, New York, N Y—"Treatment of Influenza and Respiratory Epidemics"

Dr John B Youmans, F A C P, Nashville, Tenn, spoke on "Observation on Nutrition in France," November 5, 1941, at a meeting of the College of Physicians of Philadelphia. On December 3, 1941, Dr Walter L Palmer, F A C P, Chicago, Ill, will address the College on the "Rôle of Acid Gastric Juice in Gastric and Duodenal Ulceration," and on January 7, 1942, Dr. John H Musser, F A C P, New Orleans, La, will speak on "The Heart That Is Aging"

Dr Tom D Spies, F A C P, Associate Professor of Medicine, University of Cincinnati College of Medicine, and Col W Lee Hart, F A C P, Surgeon of the 8th Corps Area, Fort Sam Houston, Tex, were among the guest speakers at the Tarrant County Medical and Surgical Clinics held in Forth Worth, Tex, October 8, 1941

The Association of American Medical Colleges held its 52nd Annual Meeting in Richmond, Va, October 27-29, 1941. Among the speakers were

George F Lull, F A C P, Colonel, (MC), U S Army—"The Place of the Medical Colleges in the National Defense Program",

Dr Alvan L Barach, F A C P, New York, N Y—"Physiological Problems Involved in Aviation Medicine"

Among the speakers at the 24th Annual Meeting of the American Dietetic Association held in St Louis, Mo, October 20-23, 1941, were

Dr Russell M Wilder, F A C P, Rochester, Minn—"Nutrition and National Defense",

Dr Seale Harris, Sr, F A C P, Birmingham, Ala—"Recent Investigations in Pellagra",

Dr Leon Schiff, F A C P, Cincinnati, Ohio—"Use of Meulengracht Diet in the Treatment of Peptic Ulcer",

Dr Harry L Alexander, F A C P, St Louis, Mo—"Allergy",

Dr John B Youmans, F A C P, Nashville, Tenn—"Observations of Health Conditions in Relation to the Food Supply and State of Nutrition of Groups in France and Spain"

The 58th Annual Meeting of the American Clinical and Climatological Association was held at Skytop, Pa, October 16-18, 1941. Among the speakers at this meeting were

Dr C Sidney Burwell, F A C P, Boston, Mass—"Relation of Some Physical Signs to Alterations in the Circulation Produced by Congenital Heart Disease",

Dr A Carlton Ernstene, F A C P, Cleveland, Ohio—"Angina Pectoris in Young Individuals with Aortic Insufficiency",

Dr William S McCann, F A C P, Rochester, N Y—"Use of Concentrated Plasma Protein Solutions in Congestive Heart Failure",

Dr Francis M Rackemann, F A C P, Boston, Mass—"Intrinsic Asthma",

Dr Lay Martin, F A C P, Baltimore, Md—"Studies on Regional Enteritis and Some Other Conditions Causing Prolonged Partial Obstruction of the Small Intestine"

The Aero Medical Association of the United States held its 13th Annual Meeting in Boston, Mass, October 31-November 2, 1941. Speakers at this meeting included

Dr Jan H Tillisch (Associate), Rochester, Minn—"The Physical Maintenance of Transport Pilots",

Irving Ershler (Associate), Lieutenant, (MRC), U S Army—"Circulatory Responses to Anoxia in Man"

John R Poppen, F A C P, Commander, (MC), U S Navy, was installed as President of the Association at this meeting

Dr John A Toomey, F A C P, Cleveland, Ohio, spoke on "Diagnosis of Poliomyelitis" and Dr Archibald L Hoyne, F A C P, Chicago, Ill, spoke on "Principles of Treatment of the Acute Stage of Poliomyelitis" at a symposium on poliomyelitis conducted by the Chicago Medical Society on October 15, 1941

Dr Walter F Donaldson, F A C P, Secretary of the Medical Society of the State of Pennsylvania, Pittsburgh, was recently cited to receive one of the Merit Awards of Northwestern University. The citation on the award reads "In recognition of worthy achievement which has reflected credit upon Northwestern University and each of her alumni"

Dr Elliston Farrell (Associate) has been appointed Assistant Professor of Tropical Medicine at Tulane University of Louisiana School of Medicine at New Orleans. Formerly, Dr Farrell was Assistant Clinical Professor of Medicine at Long Island College of Medicine Brooklyn

The New England Postgraduate Assembly, sponsored by the state medical societies of Massachusetts, New Hampshire, Rhode Island, Maine, Vermont and Connecticut, was held at Harvard University, October 29-30, 1941. Dr J Burns Amberson, Jr, F A C P, Professor of Medicine, Columbia University College of Physicians and Surgeons, New York, and Dr. George W Thorn, F A C P, Associate Professor of Medicine Johns Hopkins University School of Medicine, Baltimore, were among the speakers at this meeting

Dr Harold M Coon, F A C P, Statesan, Wis, has been appointed Superintendent of the Wisconsin General Hospital and the Wisconsin Orthopedic Hospital for Children, Professor of Hospital Administration and Executive Secretary of the University of Wisconsin Medical School, Madison, succeeding Dr Robin C Buerki, who was recently appointed Dean of the University of Pennsylvania Graduate School of Medicine and Director of Hospitals of the University of Pennsylvania, Philadelphia

On October 14, 1941, Dr Charles R Castlen, F A C P, Glendale, Calif, spoke on "Present Day Concepts of Tuberculosis in Pregnancy" at a joint meeting of the Los Angeles Obstetrical and Gynecological Society and the Trudeau Society of Los Angeles

Dr Francis J Braceland, F A C P, Dean of Loyola University School of Medicine, Chicago, participated in a symposium on "Current Trends in Neuropsychiatry" at the University of Illinois College of Medicine, October 11, 1941

Harry G Armstrong, F A C P, Major, (MC), U S Army, will deliver the Gehrman Lectures for 1941-42 of the University of Illinois College of Medicine. On October 21 and 22 Major Armstrong lectured on "Medicine in Aviation," "Selection and Care of Fliers" and "Effects of Flight on Man"

On October 3, 1941, Major Henry M Thomas, Jr, F A C P, Chief of the Medical Section, Station Hospital, Fort George G Meade, Md, addressed the Baltimore City Medical Society on "The Health of Selectees in Training," and Dr Robert H Riley, F A C P, State Health Director, Baltimore, Md, spoke on "Public Health Aspects of Selective Service"

The meeting of the New York Academy of Medicine on October 2, 1941, was devoted to the memory of the late Sir Frederick G Banting, F A C P. A memorial and scientific address on "Prevention of Diabetes from the Experimental Viewpoint" was given by Dr Charles H Best, who succeeded Dr Banting as Director of the Department of Physiology and the Banting and Best Department of Medical Research at the University of Toronto Faculty of Medicine. At this meeting Dr Elliott P Joslin, F A C P, Boston, Mass, spoke on "The Use of Insulin in Its Various Forms in the Treatment of Diabetes"

Dr Jean A Curran, F A C P, Dean of Long Island College of Medicine, Brooklyn, has been appointed Acting President of the College, succeeding Dr Frank L Babbott, who resigned

Among the speakers at the 52nd Annual Meeting of the Association of Life Insurance Medical Directors of America, held in New York, N Y, October 23-24, 1941, were

Dr Burrill B Crohn, F A C P, New York, N Y—"Achlorhydria and Its Ultimate Significance",

Dr Edgar V Allen, F A C P, Rochester, Minn—"Peripheral Arterial Diseases",

Dr Edward S Dillon, F A C P, Philadelphia, Pa—"Recent Developments in Diabetes"

The American Association of the History of Medicine held its semi-annual meeting at the University of Kansas Medical School, Kansas City, October 24-25, 1941, under the auspices of the Quivira Medical History Club of Western Missouri and Kansas. Among the speakers at this meeting were:

Dr Bert F Keltz, F A C P, Oklahoma City, Okla—"Indian Medicine in the Southwest",

Dr Thor J Jager (Associate), Wichita, Kan—"Bibliographic Notes on Claude Bernard",

Dr William S Middleton, F A C P, Madison, Wis—"Medicine at Valley Forge",

Dr. Richard M Burke (Associate), Clinton, Okla—"Significant Dates in the History of Tuberculosis"

Dr Logan Clendening, F A C P, Kansas City, Mo, presented an exhibit of early American medical journals, and Dr. Edward H Hashinger, F A C.P, Kansas City, Mo, an exhibit of early nursing bottles and pap dishes

Dr Christopher C Shaw, F A C P, Bellows Falls, Vt, has been on active duty as Lieutenant Commander in the Medical Corps of the U S Naval Reserve, assigned to the Naval Air Station, Pensacola, Fla. On September 30, 1941, he was graduated from the School of Aviation Medicine and immediately thereafter appointed an Instructor in Cardiology on the faculty of the School

Dr. Joseph H Barach addressed the Ohio County Medical Society at Wheeling, W Va, on October 10, 1941. His subject was "Treatment of Diabetes Since the Advent of Insulin". On October 14, he addressed the Elk County Medical Society at St Marys, Pa, on "Treatment of Diabetes by the General Practitioner of Medicine". On October 15, 1941, Dr Barach addressed the Crawford County Medical Society at Meadville, Pa, on the subject "Diabetes as a Scientifically Treated Disease"

CIVIL SERVICE COMMISSION SEEKING NURSES FOR SERVICE IN PANAMA CANAL ZONE

The Civil Service Commission has announced a special examination to recruit nurses for work in the Panama Canal. No written test will be given, and applications will be accepted at the Commission's Washington office until further public notice.

The entrance salary is \$1687.50 a month with provision for promotions at stated intervals. Appointments will be made to general staff duty and psychiatric work.

Applicants must not have passed their thirty-fifth birthday. Further information and application forms may be obtained from the Commission's representative in any first- or second-class post office or from the central office in Washington, D C.

*OBITUARIES***DR WARREN HORACE FAIRBANKS**

Dr Warren Horace Fairbanks was born in Newaik, Vt, on February 28, 1884. He received his early education in St Johnsbury, Vt, and then prepared for the Methodist ministry at Boston University. After spending several years as pastor of a church in Philadelphia, he decided to study medicine, and was graduated at the age of thirty-two from New York Homeopathic Medical College and Flower Hospital. Dr Fairbanks then interned at the Ann May Memorial Hospital, Spring Lake, N J, 1916-17, and in the succeeding years, having developed an interest in chest diseases, took postgraduate courses at the Trudeau School of Tuberculosis and at Colorado Springs. Upon returning to practice at Freehold, N J, in 1926, he was made Attending Physician to the Tuberculosis Preventorium at Farmingdale, N J, and its Medical Director in 1937, a position which he has held ever since. At the time of his death he was also Medical Director of Allenwood Sanitarium and Monmouth County Hospital for Tuberculosis, and Attending Phthisiologist to the Fitkin Memorial Hospital. His medical societies included the New Jersey State Society, the American Medical Association, the National Tuberculosis Association and the National Sanitarium Association. He was a Past President of the Monmouth County Medical Society, and had been a Fellow of the American College of Physicians since 1931.

Dr Fairbanks took a deep interest in the affairs of his community and was widely known as a public speaker. He collected antiques, and was especially interested in American pewter. When more leisurely days came they were apt to be given over to fishing or shooting.

Dr Fairbanks suffered a cerebral hemorrhage and died August 5, 1941, at the age of fifty-seven.

GEORGE H LATHROPE, M D, F A C P,

Governor for New Jersey

DR AUSTIN B JONES

Dr Austin B Jones was born in Shackelford, Mo, October 1, 1891. He died at his home in Kansas City, Mo, September 3, 1941.

Dr Jones attended the Missouri Valley College, Marshall, Mo, and later entered the St Louis University School of Medicine, where he received his M D degree in 1915. He served one year's internship at the City Hospital, St Louis, and then returned to Shackelford, where he practiced until 1919, when he located in Kansas City, Mo.

Dr Jones was a Diplomate of the American Board of Internal Medicine, a member of the Jackson County Medical Society, Missouri State Medical Society, the American Medical Association, and had been a Fellow of the American College of Physicians since 1928.

Dr Jones, familiarly known to all his devoted friends as "A B," was a real student, a hard worker and an honest, straightforward physician. He was absolutely ethical and would not associate with a physician that was unethical. The medical profession, as well as Kansas City, has lost a very capable physician and a grand fellow.

A C GRIFFITH, M D , F A C P ,
Governor for the State of Missouri

DR MARION LEE COMPTON

Dr Marion Lee Compton, F A C P , of the Veterans Administration Facility at Augusta, Ga , died of heart disease March 27, 1941. The appearance of his obituary in this journal has been unintentionally delayed by failure of the local College officer to submit it for publication.

Dr Compton was born at Forth Worth, Tex , August 19, 1894. He received his medical training at the University of Texas School of Medicine, graduating in 1917, thereafter pursuing postgraduate study in psychiatry and neurology at St Elizabeth's Hospital, Washington, D C. Dr Compton was the Medical Officer at the Veterans Bureau at Dallas, Tex , 1919-1923, at Little Rock, Ark , 1924-1931, and at Lyons, N J , 1931-1934. He became Clinical Director of the Veterans Administration Facility at Lexington, Ky , 1934-35, Medical Supervisor, Neuropsychiatric Service, U S Veterans Administration, 1935-39, and then Manager of the Veterans Administration Facility at Augusta from 1939 to the time of his death. During the World War he served as a First Lieutenant in the Medical Corps of the U S Army at Camp Travis, Tex. He was a member of the American Psychiatric Association and had been a Fellow of the American College of Physicians since 1935.

DR GEORGE KINGSLEY OLMSTED

Dr George Kingsley Olmsted, F A C P , of Denver, Colo , died June 25, 1941, of coronary thrombosis and diabetes mellitus. He was born in Chicago, Ill , October 16, 1871, attended Oberlin College, 1890-92, received his Ph B from Colorado College in 1894, his Ph D from Yale University in 1898, and his M D degree from Denver and Gross College of Medicine in 1903.

For many years Dr Olmsted was on the faculty of the Denver and Gross College of Medicine and the University of Colorado School of Medicine. He was a Lieutenant Colonel (Retired) in the Medical Reserve Corps of the U S Army, and a member of the staff of the Denver General, St Luke's, and Physicians and Surgeons Hospitals, a member of the Denver Medical Club, City and County Medical Society of Denver, Colorado State Medical Society, Colorado Tuberculosis Association, formerly President of the Colorado State Board of Health, and had been a Fellow of the American College of Physicians since 1924.

DR RALEIGH WILLIAM BAIRD

Dr Raleigh William Baird, F A C P , of Dallas, Tex , died July 13, 1941 He was born in Shreveport, La , in 1870, received his A B degree from Southwestern University in 1893, and his M D degree from Bellevue Hospital Medical College, New York City, in 1896 He interned at the Bellevue Hospital for a period of two years

For many years Dr Baird was Visiting Physician to the Baylor University Hospital and Chief of the Medical Department of the Dallas Medical and Surgical Clinic Hospital He was a member of his county and state medical societies, the Southern Medical Association, Fellow of the American Medical Association, and had been a Fellow of the American College of Physicians since 1921

1942 PROGRAM OF INTENSIVE POSTGRADUATE COURSES ARRANGED BY THE AMERICAN COLLEGE OF PHYSICIANS

THE Advisory Committee on Postgraduate Courses, with the approval of the Committee on Educational Policy and the Executive Committee of the College, announces the following courses, arranged through the generous cooperation of the directors and the institutions at which the courses will be given.

This is the fifth year of this activity by the College. The courses are organized especially for Fellows and Associates of the College, but where facilities are available, courses will be open to those with adequate preliminary training who are now preparing either to meet the requirements of membership in the College or certification by the American Board of Internal Medicine.

The courses are made available by the College to its members at minimum cost, because the College assumes full responsibility for promotion, advertising, printing and registration. The College continues its program of giving courses in mid-winter in addition to those arranged immediately preceding its Annual Session in April. Eventually the program may be extended to include courses at other seasons of the year also, if the demand for such courses justifies such extension.

Fees—The registration fee, regardless of the institution or course selected, is based on \$20.00 for each week. One-half of the total registration fee for any course shall be paid at time of registration, and the balance shall be paid not later than one week in advance of the opening of any course. The advance payment may be refunded by the College to any registrant who for adequate reason is unable to pursue the course, provided notice of withdrawal is registered ten days in advance of the opening of the course. Checks should be drawn to the order of "W. D. Stroud, Treasurer," and mailed to E. R. Loveland, Executive Secretary, American College of Physicians, 4200 Pine Street, Philadelphia, Pa. All tuition fees received by the College are transferred in bulk sum to the institution or director and faculty of each course.

Registration—Inasmuch as this is a general announcement of the courses without the detailed outlines of courses and the lists of officers of instruction, the more complete and final bulletin for each course will be issued at a somewhat later date. An official registration form will accompany that bulletin. Registrations will be accepted in order of receipt. The maximal registration indicated for each course must be strictly adhered to.

The College will record all registrations with the respective institutions offering courses. A matriculation card will be sent to each registrant when his fee has been paid in full.

COURSE NO 1—ALLERGY
(February 2-14, 1942)

The Roosevelt Hospital, Department of Allergy,
New York, N Y

ROBERT A COOKE, M D , F A C P , *Director*
(Minimal Registration, 6, Maximal Registration, 8)

Fee, \$40 00

This course essentially will be a repetition of the courses given under the auspices of the College by Dr. Cooke in 1940 and 1941. It will be devoted to the practical and theoretical aspects of allergy. There will be clinics, conferences, laboratory work and demonstrations. Such conditions as asthma, perennial and seasonal (hay fever) coryza, urticaria, angioedema, eczema, dermatitis, gastrointestinal and cerebral allergies, vernal catarrh and periarteritis nodosa will be presented and studied in the clinic and laboratory. Practical work will consist of history taking, physical examinations, skin testing—direct and by passive transfer, and various laboratory procedures. The laboratory will take up preparation of allergens, Dale reactions, bacterial and mold cultures, preparation of autogenous vaccines, vital capacity studies, etc.

Registrants may obtain their lunches at the hospital.

COURSE NO 2—THE DIAGNOSIS AND TREATMENT OF
HEART DISEASE
(February 2-14, 1942)

Massachusetts General Hospital and the House of the Good Samaritan,
Boston, Mass

PAUL D WHITE, M D , F A C P , *Director*
(Minimal Registration, 20; Maximal Registration, 30)

Fee, \$40 00

The course will cover the fundamentals in the diagnosis and treatment of disorders of the heart and circulation. Approximately half of the time will be devoted to demonstrations and small group instruction in pathology, electrocardiography, roentgenology, and the study of heart sounds and murmurs in the clinics and wards of the Massachusetts General Hospital and at the House of the Good Samaritan. The remainder of the time will be devoted to clinics and clinical-pathological discussions of special phases of heart disease and its treatment, conducted by members of the Massachusetts General Hospital staff and by members of other hospital staffs in Boston particularly qualified to discuss their subjects.

COURSE NO 3—GENERAL MEDICINE
(February 2-14, 1942)

University of California Medical School and Stanford University
of Medicine, San Francisco, Calif

WILLIAM J KERR, M D , F A C P , *Director*
STACY R METTIER, M D , F A C P , *Associate Director*
University of California Medical School

ARTHUR L BLOOMFIELD, M D , F A C P , *Director*
DWIGHT L WILBUR, M D , F. A C P , *Associate Director*
Stanford University School of Medicine

(Minimal Registration, 20, Maximal Registration, not limited)

Fee, \$40 00

This course is designed to give a survey of the recent developments in all phases of general medicine. Related topics will be presented in the form of symposia. The lectures and discussions will be supported by clinics, ward demonstrations and clinical, pathologic and radiologic conferences. Emphasis will be placed on some of the newer drugs, such as the sulfonamide preparations, and on endocrine products. Round table discussions will include diseases of the gastrointestinal tract, the cardiovascular system and the respiratory tract. Attention will be given to new aspects of nutrition and of psychosomatic relationships in medicine. There will be a symposium on new diagnostic procedures as well as on the treatment of diseases of the blood.

The meetings will be held at the University of California Hospital, the Stanford University Hospitals and the San Francisco Hospital.

COURSE NO 4—INTERNAL MEDICINE
(February 2-14, 1942)

Johns Hopkins University School of Medicine and University of Maryland
School of Medicine, Baltimore, Md

WARFIELD T LONGCOPE, M D , F A C P , *Dnector*
GEORGE W THORN, M D , F A C P , *Associate Dnector*
Johns Hopkins University School of Medicine

MAURICE C PINCOFFS, M D , F A C P , *Dnector*
H RAYMOND PETERS, M D , F A C P , *Associate Director*
University of Maryland School of Medicine

(Minimal Registration, 20, Maximal Registration, 50)

Fec, \$40 00

The Johns Hopkins University School of Medicine in collaboration with the University of Maryland School of Medicine will offer a Postgraduate Course of Instruction in Chemotherapy, Hematology, Nutrition and Endocrinology Each of the subjects will be allotted approximately one-fourth of the total available time

Instruction in Chemotherapy will consist of a systematic review of the chemotherapy of bacterial infections which will be presented in six three-hour sessions This review will cover the following subjects pharmacology of the sulfonamide drugs, their mode of action, methods of administration, toxicology, the rôle of immunity in response to chemotherapy, sulfonamide therapy in pneumonia, streptococcal infections, meningitis, gonococcal infections, urinary tract infections, bacillary dysentery, staphylococcal infections, etc The subject matter will be presented in a series of lectures and clinics supplemented by round table discussion

Instruction in Hematology will include a systematic survey of the field with particular emphasis on recent developments An essential feature of the course will be provision for individual study of the blood of representative hematological diseases with a discussion of interpretation, diagnosis and treatment *Physicians will be required to provide their own microscopes*

A session will be devoted to transfusions of blood, of plasma and of blood substitutes Problems connected with reactions to transfusions will be discussed The administration of blood banks will be considered

Instruction in Nutrition will be concerned primarily with a discussion of recent advances in our knowledge of the metabolism of minerals and vitamins Mineral and vitamin deficiencies will be considered in lectures and demonstrations under the following headings physiological importance, clinical manifestations of deficiency, methods of detection and treatment

Instruction in Endocrinology will include studies of the chemical nature and physiological action of the various hormones Clinical manifestations

of disturbances in adrenal, gonadal, pancreatic, parathyroid, pituitary and thyroid functions will be illustrated in clinics and discussed at round table conferences. The relative efficacy of specific hormone preparations will be considered. Particular attention will be directed to a discussion of tests which have proved their usefulness in the differential diagnosis of endocrine disorders. It will be possible for small groups of physicians to participate in the daily ward visits on the Clinical Metabolic Unit of the Johns Hopkins Hospital.

At the Johns Hopkins University School of Medicine the instruction will be supervised not only by Drs Longcope and Thorn, Director and Associate Director of the course, but also by Drs M M Wintrobe, Associate in Medicine, and W Barry Wood, Associate in Medicine.

COURSE NO 5—GASTROINTESTINAL DISEASES (February 2-7, 1942)

Graduate Hospital, University of Pennsylvania,
Philadelphia, Pa

HENRY L BOCKUS, M D , F A C P , *Director*

(Minimal Registration, 20, Maximal Registration, 48)

Fee. \$20 00

Faculty. Thirty members of the Faculty of the Graduate and Undergraduate Schools of Medicine of the University of Pennsylvania.

A number of symposia have been arranged in order to emphasize recent advances in the diagnosis and treatment of various digestive tract disorders. These symposia include:

- (1) Value of Liver Function Tests in Diagnosis and Treatment,
- (2) Diagnosis of Chronic Gastritis,
- (3) Colonic Disorders,
- (4) Diseases of the Esophagus,
- (5) The Relationship of Nutritional Deficiency to Alimentary Tract Disease,
- (6) Functional Diseases of the Digestive Tract,
- (7) Regional Enteritis and Enterocolitis;
- (8) Pancreatic Disorders;
- (9) Peptic Ulcer;
- (10) Achlorhydria

The course includes six hours of practical demonstrations of gastroscopy, sigmoidoscopy, bile microscopy, intestinal parasites, coprology and liver function tests. Several periods of ward round demonstrations of interesting cases and of clinical pathological conferences are included in the schedule.

Time: 8 30 a m to 5 30 p m , Monday to Friday inclusive Saturday,
9 00 a m. to 1 00 p m

COURSE NO 6—ALLERGY
(April 6-18, 1942)

Washington University School of Medicine and
Barnes Hospital, St Louis, Mo

HARRY L ALEXANDER, M D , F A C P , *Director*
(Minimal Registration, 6, Maximal Registration, 8)
Fee, \$40 00

The purpose of this course is to review intensively the subject of clinical allergy in both its theoretic and practical aspects. Informal lectures, clinics, demonstrations and examination of patients will be devoted to the study of asthma, hay fever, allergic rhinitis, urticaria, eczemas, gastrointestinal and other manifestations of allergy.

Laboratory procedures will include demonstrations and practice of the preparation of allergens and autogenous vaccines, skin testing, cytologic examination of sputum and nasal secretion and vital capacity determinations.

Practical work on assigned cases will consist of history taking, physical examination, skin testing, examination of secretions, and other relevant laboratory work.

COURSE NO 7—ARTHRITIS AND RHEUMATIC DISEASES
(April 13-18, 1942)

The Mayo Foundation, University of Minnesota, and
The Mayo Clinic, Rochester, Minn

PHILIP S HENCH, M D , F A C P , *Director*
(Minimal Registration, 20, Maximal Registration, 35)
Fee, \$20 00

This course will cover the diagnosis and treatment of the commoner diseases of muscles and joints, including muscular rheumatism, rheumatoid arthritis and osteo-arthritis. Special emphasis will be placed on the treatment of gonorrheal arthritis by the sulfonamides, the treatment of rheumatoid arthritis by gold salts, the diagnosis and treatment of gout, the treatment of suppurative arthritis and war wounds of joints.

Members of the staff of The Mayo Clinic and invited guest speakers will conduct the course under the supervision of Dr Philip S Hench and Dr Charles H Slocumb, of the service for rheumatic diseases at The Mayo Clinic.

COURSE NO 8—PERIPHERAL VASCULAR DISEASES,
INCLUDING HYPERTENSION

(April 6–18, 1942)

The Mayo Foundation, University of Minnesota, and
The Mayo Clinic, Rochester, Minn

EDGAR V ALLEN, M D , F A C P , *Director*

(Minimal Registration, 35; Maximal Registration, 100)

Fee, \$40 00

This course will include a discussion of the physiology of the peripheral circulation, the syndrome of hypersensitive carotid sinus, occlusion of the inferior and superior vena cava, temperature of the skin as a measure of peripheral circulation, consideration of nail fold capillaries, venous pressure, venography and infra-red photography, erythromelalgia, colorimetry, symptoms of peripheral vascular disease, cervical rib and scalenus syndrome, graphic and audible recording of arterial murmurs, studies on the speed of arterial circulation, thromboangitis obliterans, terminology and examination in peripheral vascular diseases, periarteritis nodosa and "vascular allergy," arteriosclerosis obliterans, aneurysm and arteriovenous fistula, sudden arterial occlusion, diseases of minute blood vessels, temporal arteritis and cold allergy, glomus tumor, varicose veins, phlebitis and other diseases of the veins, methods of investigation in peripheral vascular diseases and their clinical value, critical consideration of some methods of treatment of peripheral vascular diseases, differential diagnosis in edema of the extremities, lymphedema, pulmonary hypertension, systemic hypertension, the retinae in hypertension, normal blood pressure and its physiologic variations, prediction of the development of hypertension, classification of essential hypertension, hypertension and pregnancy, paroxysmal hypertension, arterioles in hypertension, treatment of hypertension, orthostatic tachycardia and hypotension, renal insufficiency in hypertension, the electrocardiogram in hypertension, congestive heart failure due to hypertension, experimental hypertension, history and results of treatment of hypertension with kidney extract, occupation and vascular diseases, shock, arteriosclerosis and other conditions

Instruction will be furnished by thirty-five physiologists, surgeons, internists and pathologists, including several nationally recognized guest speakers. Formal presentations, conferences and clinics will be given

COURSE NO 9—GASTROINTESTINAL DISEASES**(April 6–18, 1942)****University of Chicago, The School of Medicine,
Billings Hospital, Chicago, Ill****WALTER L PALMER, M D , F A C P , *Dnector*****(Minimal Registration, 30, Maximal Registration, 75)****Fee, \$40 00**

The purpose of this course is to review the field of Gastro-enterology with particular reference to the etiology, pathogenesis, diagnosis and treatment of the diseases of the digestive tract. The program will consist chiefly of lectures and discussions given by authorities in the various subjects. Ample opportunity for discussion will be allowed and encouraged.

Lectures will be given in Room M-137 of the Department of Medicine at the University of Chicago, Billings Hospital. Registrants should report to this room when the course opens.

COURSE NO 10—INTERNAL MEDICINE**(April 6–18, 1942)****University of Minnesota Medical School, Minneapolis, Minn****CECIL J WATSON, M D , F A C P , *Dnector*****(Minimal Registration, 30, Maximal Registration, 50)****Fee, \$40 00**

The continuation course in Internal Medicine will be given at the Center for Continuation Study, University of Minnesota. It will be of interest to members of the American College of Physicians, qualified physicians who plan to apply for admission to the College, prospective candidates for the American Board of Internal Medicine and such other physicians who limit their practice mainly to Internal Medicine and are eligible for admission under the regulations.

The course will be presented in seven sections: cardiovascular diseases, hematology, metabolism and endocrinology, infectious diseases, diseases of the gastrointestinal tract, pulmonary diseases and deficiency states. The teaching program will consist of lectures, movies, clinics, demonstrations and round table question and answer discussion periods. Mimeographed outlines of lectures and demonstrations will be supplied without extra charge. Unless otherwise specified all classes will be held in the Center for Continuation Study. Bus transportation will be furnished to all off-campus clinics and demonstrations. A faculty of over forty teachers is being assembled.

from the graduate school staff in Minneapolis and St. Paul and The Mayo Foundation. In addition, distinguished teachers from other centers will take part. Each part of the course will be presented by men who have given special attention to that sub-division of the subject.

The group will live in the Center for Continuation Study where pleasant, comfortable rooms and good meal service are available. Rooms are from \$6.25 to \$8.75 a week. Meals are \$1.75 a day. Parking in the Center for Continuation Study garage is \$0.50 a day. There will be a luncheon each day at which members of the faculty will conduct discussion periods. Tea will be served at four o'clock. Medical movies will be shown in the lounge after dinner. The registrants will be able to make full use of the medical library facilities of the general library of the University of Minnesota, which is located just a short distance from the Center for Continuation Study. Recreation periods will be held on Wednesday and Saturday afternoons.

The course will start at 9:00 a.m., April 6, and close at 2:00 p.m., April 18, 1942. A certificate of attendance will be issued by the University of Minnesota to all who attend the prescribed number of exercises.

COURSE NO. 11—TUBERCULOSIS

(April 13–18, 1942)

University of Colorado School of Medicine and Hospitals,
Denver, Colo.

JAMES J. WARING, M.D., F.A.C.P., *Director*

(Minimal Registration, 10; Maximal Registration, 25)

Fee, \$20.00

The purpose of this course is to review the most important clinical features of all stages of pulmonary tuberculosis. Complications of tuberculosis, especially tracheo-bronchial tuberculosis and tuberculous effusions, with and without pneumothorax, will be presented for discussion. Demonstrations will be given of the tuberculin reaction and laboratory methods of diagnosis by animal inoculation and culture of the tubercle bacillus. The class will have the opportunity daily to examine many patients with minimal, moderately advanced and far advanced tuberculosis, many patients with silicosis, patients suitable for varied forms of collapse therapy, patients after phrenic operation, patients taking artificial pneumothorax, patients being treated by the Monaldi method for closure of cavity, patients after thoracoplasty, after lobectomy and after pneumonectomy. Conferences centered around roentgen-ray films will be held daily.

ANNALS OF INTERNAL MEDICINE

VOLUME 15

DECEMBER, 1941

NUMBER 6

THE CLINICAL SYMPTOMS AND SIGNS OF VITAMIN B COMPLEX DEFICIENCY ¹

By WILLIAM H SEBRELL,† M D , F A C P , *Bethesda, Maryland*

THE symptoms caused by deficiencies in various members of the vitamin B complex probably constitute our greatest medical problem in the deficiency field. There are eight known substances which may be called members of the vitamin B complex. These are thiamin, riboflavin, nicotinic acid, pyridoxine, pantothenic acid, p-aminobenzoic acid, choline and inositol. At least four of these appear to be needed by man. These are thiamin, riboflavin, nicotinic acid and pyridoxine. Deficiencies in the remaining known members of the B complex have been shown to cause various symptoms in experimental animals.

It has been shown that a deficiency in pantothenic acid causes a graying of the hair in black rats, and Daft and Sebrell ¹ have found that a hemorrhagic necrosis of the adrenal glands in rats is caused by a deficiency in pantothenic acid. Further observations on patients are necessary to determine whether or not this substance is needed by man.

A deficiency in choline causes a fatty liver, and it appears quite likely that this also may be a human essential.

It has been reported that a deficiency in inositol causes a loss of hair in mice, and Ansbacher ² has very recently reported that a deficiency in p-aminobenzoic acid causes graying of hair in black rats. The possible clinical importance of deficiencies in these substances remains to be determined. In addition, these eight substances probably do not represent the entire vitamin B complex. Evidence based on animal experimentation indicates that other unidentified substances probably are present.

* Read at the Boston meeting of the American College of Physicians, April 23, 1941.

† Chief, Division of Chemotherapy, National Institute of Health, U S Public Health Service, Bethesda, Maryland

Spies, Bean and Ashe³ have furnished us with clinical evidence on human pyridoxine deficiency. They report symptoms of weakness and difficulty in walking which they were able to correlate with a low excretion of pyridoxine and which improved under treatment with pyridoxine. Spies, Hightower and Hubbard⁴ and Jolliffe⁵ also have independently reported that pyridoxine is beneficial in controlling some of the symptoms of paralysis agitans although it cannot be regarded as a specific for this disease. We have treated approximately 30 very old and severe cases of paralysis agitans with large doses of pyridoxine without any apparent benefit. It appears to be definitely indicated that in early cases of paralysis agitans it should be given thorough trial.

There is a wealth of clinical data on the symptomatology of thiamin, nicotinic acid and riboflavin deficiency. Sydenstricker has discussed the symptoms of multiple deficiencies which are so commonly seen in the clinic.

All of you are familiar with the gross symptoms of extreme thiamin deficiency such as enlargement of the heart, extreme edema, tenderness of the calf muscles, weakness, hyperesthesia and neuritis which characterize beriberi. It is the less extreme forms with which we are particularly concerned in the United States. Soma Weiss and Wilkins⁶ and Dustin, Weyler and Roberts⁷ have directed special attention to heart changes. Goodhart and Jolliffe^{8,9} have called attention to the peripheral neuritis occurring as a complication of alcoholism, and other diseases in which there is interference with thiamin intake or utilization. More recently the experimental work of Williams, Mason, Wilder and Smith¹⁰ has directed attention to a group of symptoms hitherto undescribed in early thiamin deficiency. Their observations, made under controlled conditions, have shown that the early symptoms of thiamin deficiency may be undue anxiety, weakness, lack of interest and a group of mental symptoms which would ordinarily be diagnosed as neurosis. The possible significance of thiamin deficiency in conditions such as these is of the greatest clinical importance, especially since all of the dietary data available to us indicate that thiamin-deficient diets are very prevalent in our population. The best opinion now is that normal adults require about 1.8 milligrams of thiamin a day.

The symptoms of nicotinic acid deficiency as characterized by the typical lesions of pellagra are also quite familiar. The dermatitis which may be bullous, resembling in many ways the early stages of a severe sunburn, appears most frequently either on exposed surfaces or in regions subject to irritation. However, there are many cases of nicotinic acid deficiency which have minimal skin lesions or no skin lesions at all. These cases most frequently show loss of weight, weakness, mental depression, and gastrointestinal upset with indigestion and sometimes diarrhea. There is usually a reduction or absence of hydrochloric acid in the stomach. In the stomatitis which also is frequently found in these cases the tongue is usually red and there may be extensive ulceration, the buccal lesions usually swarm with

organisms of the Vincent's type which may lead to an incorrect diagnosis of Vincent's angina as reported by King¹¹. The patients usually complain of a burning or scalded sensation in the mouth. In addition to this type of the disease, Cleckley, Sydenstricker and Geeslin¹² and Jolliffe, Bowman, Rosenblum and Fern¹³ have independently described an acute mental manifestation of nicotinic acid deficiency in which no skin lesions are seen. These patients are either chronic alcoholics or old people in whom there is a severe mental disturbance similar in many respects to cerebral arteriosclerosis. They show delirium, an extreme mental confusion, and disorientation. They may have sucking reflexes and cog wheel rigidities. These cases are thought to represent an acute nicotinic acid deficiency and seem to require large doses of nicotinic acid intravenously, following which they rapidly return to normal, where formerly the death rate was extremely high. The normal adult requirement for nicotinic acid is probably about 18 milligrams daily.

The symptoms of human riboflavin deficiency were not recognized as a separate entity until late in 1938⁴. Since then several reports have appeared indicating that the condition is rather common. The typical lesion is a macerated linear fissure in each angle of the mouth similar to a lesion which earlier had been called an angular stomatitis. However, the entire lip is also involved. The lips become scaly, appear to be chapped, and are shiny, reddened and denuded in appearance, especially along the line of closure. For this reason the entire lip lesion has been designated cheilosis. In many cases we also have seen a superficially eroded lesion located just inside the nares. A fissure may also occur in this area at the mucocutaneous junction. The tongue takes on a red or slightly purplish color and can be distinguished from the bright red tongue of pellagra. Many cases have a seborrheic dermatitis of varying extent which may be exceedingly mild, involving only the fold around the nares or the eyes. These lesions consist of small greasy scales on a slightly erythematous base. In some instances the ears and other folds of the body are involved.

Some observers have found cases in which there were hard seborrheic plugs across the bridge of the nose which have been designated as "shark skin". It was noted by Spies and his associates¹⁵ that many cases had eye symptoms such as photophobia and lacrimation, with reddening of the conjunctiva. Bessey and Wolbach¹⁶ found vascularization of the cornea to be the earliest and most important manifestation of riboflavin deficiency in the rat, and Eckardt and Johnson¹⁷ have reported a high incidence of keratitis in rats on riboflavin deficient diets. In retrospect it appears that the lesions of riboflavin deficiency were confused with pellagra in the older literature and were diagnosed as pellagra *sine pellagra*. There are many references in the older literature to eye lesions accompanying pellagra. The very early writers on pellagra, such as Soler¹⁸ (1791) and Rampoldi¹⁹ (1795), refer to such eye symptoms as inflammation of the cornea, corneal ulcers, and opacities. Photophobia, mydriasis, conjunctivitis, pain, failing

vision, and superficial inflammation of the cornea have been described by other writers on pellagra. It seems not unlikely now that in view of the close association frequently seen between riboflavin deficiency and pellagra, many of these lesions may have been due to riboflavin deficiency. Spies, Vilter and Ashe²⁰ have called attention to such lesions and stated that more than 70 per cent of the patients in their nutrition clinic with frequent recurrences of pellagra, beri beri, or riboflavin deficiencies, also have visual disturbances. Spies, Bean and Ashe¹⁵ noted that these disturbances disappeared in from four to six days following the administration of riboflavin. Following the demonstration by animal experimentation that keratitis was a manifestation of riboflavin deficiency in the rat, and the clinical demonstration by Spies and his associates that certain eye symptoms clear up on the administration of riboflavin, Kruse, Sydenstricker, Sebrell and Cleckley²¹ demonstrated that 47 patients with symptoms of photophobia, dimness of vision, burning sensation and circumcorneal injection, mydriasis, and iritis showed slit lamp evidence of a vascularizing keratitis. In these patients, there was spectacular improvement following the administration daily of 5 to 15 milligrams of riboflavin. Also, repeated slit lamp examination showed rapid resolution of the keratitis and emptying of the vessels in the cornea.

Johnson and Eckardt²² have also demonstrated that riboflavin is of value in the treatment of rosacea keratitis. It therefore appears that keratitis is definitely a part of the syndrome caused by riboflavin deficiency.

Sebrell, Butler, Wooley and Isbell²³ have recently reported an extensive study on riboflavin balance. These studies indicate that there is very rapid decrease in the urinary excretion of riboflavin following a decreased intake in the diet. They also show that the human riboflavin requirement is approximately 3 milligrams per day for an adult woman. This quantity of riboflavin can be obtained from a liberal diet. In the treatment of riboflavin deficiency I would recommend the use of not less than 6 milligrams per day and up to 15 milligrams. Some cases seem to respond rather slowly to therapy. It is not to be supposed that all cases having fissures at the angles of the mouth are due to riboflavin deficiency. Pollack²⁴ has recently seen such cases due to ill fitting dentures, bearing no relation to riboflavin deficiency.

There is evidence to indicate that the above deficiency diseases are of the utmost clinical importance in the United States and Dr Wilder has already discussed the nutrition program which is designed to help prevent these deficiencies. Dietary survey data show that there are large numbers of people living on diets which do not contain enough thiamin, nicotinic acid, or riboflavin to meet what we consider to be adequate levels of intake. This is probably reflected in an enormous number of cases with mild symptoms of each of these deficiency diseases, and it is exceedingly difficult to make an estimate of the total number. However, from the number of patients appearing

in the clinics, where special efforts are being made to recognize these conditions and the number of patients showing vague symptoms of the above types which improve on treatment with these vitamins, it is not unlikely that these deficiencies constitute one of our largest medical problems. From the point of view of preventive medicine, the evidence is conclusive that there is a great opportunity to improve the health of the nation by increasing the vitamin B complex content of the diets of a considerable part of our population.

REFERENCES

- 1 DART, FLOYD S, and SIBRELL, W H Hemorrhagic adrenal necrosis in rats on deficient diets, *Pub Health Rep*, 1939, liv, 2247
- 2 ASBACHER, S p-Aminobenzoic acid, a vitamin, *Science*, 1941, xciii, 164
- 3 SPIES, TOM D, BEAN, WILLIAM B, and ASHE, WILLIAM F A note on the use of vitamin B₆ in human nutrition, *Jr Am Med Assoc*, 1939, cxii, 2414
- 4 SPIES, T D, HIGHTOWER, D P, and HUBBARD, L H Some recent advances in vitamin therapy, *Jr Am Med Assoc*, 1940, cxv, 292
- 5 JOLLIFFE, N Clinical aspects of vitamin B deficiencies, *Minnesota Med*, 1940, xxiii, 542
- 6 WEISS, SOMA and WILKINS, ROBERT W The nature of the cardiovascular disturbances in nutritional deficiency states (beriberi), *ANN INT MED*, 1937, xi, 104
- 7 DUSTIN, CECIL C, WEYLER, HENRY and ROBERTS, C PURCELL Electrocardiographic changes in vitamin B₁ deficiency, *New Eng Jr Med*, 1939, ccxx, 15
- 8 GOODHART, ROBERT and JOLLIFTE, NORMAN Effects of vitamin B (B₁) therapy on the polyneuritis of alcohol addicts, *Jr Am Med Assoc*, 1938, cx, 414
- 9 JOLLIFFE, NORMAN and GOODHART, ROBERT Beriberi in alcohol addicts, *Jr Am Med Assoc*, 1938, cx, 380
- 10 WILLIAMS, RAY D, MASON, HAROLD L, WILDER, RUSSELL M, and SMITH, BENJAMIN F Observations on induced thiamine (vitamin B₁) deficiency in man, *Arch Int Med*, 1940, lvi, 785
- 11 KING, J D Vincent's disease treated with nicotinic acid, *Lancet*, July 13, 1940, page 32
- 12 CLECKLEY, H M, SIDENSTRICKER, V P, and GEESLIN, L E Nicotinic acid in the treatment of atypical psychotic states associated with malnutrition, *Jr Am Med Assoc*, 1939, cxii, 2107
- 13 JOLLIFFE, N, BOWMAN, K M, ROSENBLUM, L A, and FEIN, H D Nicotinic acid deficiency encephalopathy, *Jr Am Med Assoc*, 1940, cxiv, 307
- 14 SEBRELL, W H, and BUTLER, R E Riboflavin deficiency in man A preliminary note, *Pub Health Rep*, 1938, liii, 2282 Riboflavin deficiency in man (ariboflavinosis), *ibid*, 1939, liv, 2121
- 15 SPIES, T D, BEAN, W B, and ASHE, W F Recent advances in the treatment of pellagra and associated deficiencies, *ANN INT MED*, 1939, xii, 1830
- 16 BESSEY, O A, and WOLBACH, S B Vascularization of the cornea of the rat in riboflavin deficiency, with a note on corneal vascularization in vitamin A deficiency, *Jr Exper Med*, 1939, lxix, 1
- 17 ECKARDT, R R, and JOHNSON, L V Nutritional cataract and relation of galactose to appearance of senile suture line in rats, *Arch Ophth*, 1939, xxxi, 315
- 18 SOLER Osservazione medico-pratiche che formano la storia esatta di una particolare malattia chiamata pellagra, Venice, 1791, cited by HARRIS, H F Pellagra, 1919, Macmillan Company, New York.
- 19 RAMPOLDI, R La pellagra e il mal d'occhi, *Ann di ottal*, 1885, xiv, 99, cited by Harris Pellagra

- 20 SPIES, T D, VILTER, R W, and ASHE, W F . Pellagra, beriberi, and riboflavin deficiency in human beings. Diagnosis and treatment, Jr Am Med Assoc, 1939, cxiii, 931
- 21 KRUSE, H D, SYDENSTRICKER, V P, SEBRELL, W H, and CLECKLEY, H M Ocular manifestations of ariboflavinosis, Pub Health Rep, 1940, lv, 157
SYDENSTRICKER, V P, CLECKLEY, H M, SEBRELL, W H, and KRUSE, H D The ocular manifestations of ariboflavinosis A progress note, Jr Am Med Assoc, 1940, cxiv, 2437
- 22 JOHNSON, L V, and ECKARDT, R E Rosacea keratitis and conditions with vascularization of cornea treated with riboflavin, Arch Ophth, 1940, xxiii, 899
- 23 SEBRELL, W H, JR, BUTLER, R E, WOOLEY, J G, and ISBELL, HARRIS Human riboflavin requirement estimated by urinary excretion of subjects on controlled intake, Pub Health Rep, 1941, lvi, 510
- 24 POLLACK, HERBERT Unpublished data

SCARLET FEVER IMMUNIZATION *

By JOHN A TOOMEY, M D , F A C P , *Cleveland, Ohio*

THERE is need for a procedure that will actively immunize susceptibles against scarlet fever. Such immunization is necessary for the personnel of contagious disease hospitals, preventoriums and orphan asylums, it is no less necessary for the young if the complications of scarlet fever are to be avoided. However, the need may not seem apparent when it is noted that for the past 40 years scarlet fever has been increasing in morbidity, but decreasing in mortality.¹ On the other hand, everyone will admit that the severity or mildness of the infection has no bearing on the degree or type of complication which may occur.

The Dicks have described an immunizing toxin, the efficacy of which has been tested under the most adverse circumstances, i.e., among groups of nurses working in contagious disease hospitals. In such institutions, Hektoen and Johnson² reported a morbidity rate of 7.7 per cent, Place,³ as high as 8.6 per cent, Benson and Rankin,⁴ a variable rate, from 4 to 10 per cent, Anderson and Reinhardt,⁵ 12.8 per cent in known positive Dick test reactors. On an average, 12 per cent of the student nurses in this training school (City Hospital, Cleveland) have contracted scarlet fever. In 1922, the attack rate was as high as 17.7 per cent.

Over 6,000 nurses have been admitted to the School of Nursing, City Hospital, Cleveland, during the past 20 years. Out of such a group, it could be expected that at least 480 might contract scarlet fever. If one considers that five dollars a day is a minimal charge for hospital care and that the scarlet fever patient is hospitalized for 30 days, it would cost the institution about \$72,000.00 to care for such a number of cases. Not only the cost, but inconvenience to the hospital and the time lost by nurses are items of administration which have to be considered.

Since early 1925, immunization has been offered to all of our susceptible nurses. An immunization record of each student was kept. This included a record of all tests and procedures as well as past contagious and atopic diseases (figures 1 and 2).

The Dick test was performed in 4,640 nurses. Three thousand one hundred and four were found to be negative, and the remainder, 1,536, were positive reactors.

Some of our susceptible affiliate nurses (207) did not take contagious disease training, so that immunization was not compulsory.

* Read before the Twenty-fifth Annual Session of the American College of Physicians, April 25, 1941, Boston, Mass.

From the Division of Contagious Diseases, City Hospital, and the Department of Pediatrics, Western Reserve University, Cleveland, Ohio.

(over)

Fig 2

One thousand three hundred and twenty-nine susceptible nurses were actively immunized, 1,273 by injecting toxins in the old standard doses of 500, 2,000, 8,000, 25,000 and 80,000 units as recommended by the Scarlet Fever Commission, 41 received Laison's vaccine, 15 received toxin made from stock streptococci

According to the Dicks,⁶ 95 per cent of the nurses susceptible to scarlet fever can be immunized Rappaport⁷ reports that 99.5 per cent of 222 nurses became completely immunized after the injection of toxin He states that since March, 1926 (report made in 1936), no student nurse has developed scarlet fever

No cases developed among 298 susceptible nurses immunized by Anderson,⁸ whereas 15 of 449 nurses who received no immunizing doses contracted scarlet fever during the same period He and Reinhardt⁹ reported 7 failures out of 1,038 nurses immunized They analyzed the records of over 6,000 individuals and found that the attack rates for the Dick negative group and for the Dick positive group, which was later immunized, were but 0.7 per cent For the nine years included in their study, the affiliating hospitals that did not provide for immunization had a scarlet fever incidence among their nursing staffs four times as great as that found in the immunized hospitals Toyoda et al.⁹ report that among the non-immunized, 43.3 out of 1,000 persons were infected, whereas among those completely immunized, the rate was only one per 1,000 Henry¹⁰ recalls that in 1926 and for seven years thereafter there were no cases of scarlet fever that developed in physicians or nurses fully immunized The subsequent Director of Public Health of his city was persuaded to abandon the compulsory immunization program, and the disease again reappeared in the physicians and nurses Twelve cases developed among the personnel before reimmunization was started Knights¹¹ immunized a small number of nurses and decided that the results were encouraging enough to warrant continuing the immunization of nurses who gave no history of having had scarlet fever In 1934, Benson and Rankin⁴ of Edinburg detailed nine years' experience with active immunization Seven of their nurses contracted the disease, but only one of these had been immunized

Place³ reported that the majority of their nurses had been immunized since 1925 The attack rate among susceptible nurses was 8.6 per cent, between 1925 and 1936, the rate among 1,446 nurses serving in the ward was 1.3 per cent or 20 nurses Only three failures of immunization were described, one of which never became negative even after two series of injections Two of the three had positive Dick tests, one before and one at the onset of the scarlet fever, one was not tested It is significant that the drop from 8.6 per cent to 1.3 per cent in this series was not associated with a corresponding decrease of scarlet fever among nurses in general of this region One hundred and twenty-seven nurses became ill with scarlet fever and were admitted to the hospital between 1913 and 1924, during the next

12 years, there were 100 This decrease in the number of scarlet fever cases among the nurses was not due to the fact that there was a decrease in the incidence of scarlet fever; in fact, the morbidity had increased.

Not one of Platou's ¹² 164 immunized susceptible nurses had scarlet fever during a period of four years, whereas the disease developed in eight out of 150 non-affiliated students

Hektoen and Johnson ² state that not one of 200 immunized susceptibles developed scarlet fever and that of 614 nurses taken into the Service since the Dick test came into use, three or 0.5 per cent had scarlet fever Only one of their nurses developed scarlet fever since December 1, 1927 (report 1934)

RESULTS OF ACTIVE IMMUNIZATION AT CITY HOSPITAL, CLEVELAND

Not all of the 1,273 individuals immunized received the full five doses as recommended by the Scarlet Fever Commission (table 1), 155 had from one to four doses, 1,118, five or more Immunization was discontinued and the nurse received less than five doses if the reactions became too severe, if she returned to her own school or for many other reasons.

Active immunization against diphtheria as well as scarlet fever is sometimes condemned because individuals previously injected with vaccine antigens have contracted the disease Such condemnation is never merited if no effort has been made to find out whether the susceptibles have been immunized The only way one can be sure that a patient has been immunized is by doing a Dick test after the immunization procedure has been completed

The results of immunization are contained in table 1

TABLE I
Immunization

Total Number Nurses to Be Immunized	1273	Total Number of Negative Reactions	
Only 1 dose given	6	After Immunization	1181
Two doses given	46	Negative after 1 dose	1
Three doses given	49	Negative after 2 doses	34
Four doses given	54	Negative after 3 doses	31
Five doses given	1118	Negative after 4 doses	33
(29 given 2 series of injections)		Negative after 5 or more doses	1082
		Still positive	92

Eleven hundred and eighty-one or 92.7 per cent of the 1,273 susceptibles became negative reactors Ninety-two or a little over 7 per cent were still positive

Frequently, when the Dick test is repeated in immunized individuals, it may be found supposedly positive and about it will be an area of redness and induration Sometimes, a second immunizing series may be given and still the reactions are positive, often with marked local reactions Many of these results are spurious When such people are tested with control as well as Dick toxin, it may be found that the marked local reactions are due to the control rather than to the toxin itself and that the individuals actually are

negative even though they do have a marked local reaction around the injection

When, for some reason it became necessary to stop immunization short of five doses, a skin test was done at the same time it would have been performed had the nurses continued with the group in which they had started. One of the six receiving one immunizing dose had a negative reaction. Of the 155 receiving only from one to four doses, 99 seemed to have had some benefit since they became negative reactors. This does not mean that they were completely immunized, they may have been merely immunized against at least one skin test dose.

Sixty-five of the susceptible nurses contracted scarlet fever, 49 of them becoming ill during the course of immunization. Actually, only 16 given the full dose of antigen recommended developed the disease (table 2).

TABLE II	
Number Developing Scarlet Fever	
During interval between positive test and planned first immunizing dose	41
After one dose	2
" two doses	4
" three "	2
" five " or more	16

Ignoring the 49 who developed scarlet fever during or before immunization was started, there were 16 cases, or a little over 1 per cent of the total 1,273 individuals immunized, who developed the disease.

On admission to the hospital, eight of these nurses had acquired some immunity and were negative reactors to the Dick test, eight were still positive.

The case histories of these 16 cases bear analyses (table 3). In seven, the attacks were mild, in three, moderate, in five, severe, in one, the diagnosis was questionable. The reactions to the test bear no relation to the severity of the subsequent attacks of scarlet fever. Actually, eight had not been immunized, thus, there remained eight failures.

REACTIONS

Reactions occur with any kind of an immunizing procedure. Sometimes these may be as severe as the disease itself. It might be considered axiomatic that the more closely the symptoms produced by the antigen products resemble those of the disease, the better is the chance of immunizing the susceptible.

The reactions to scarlet fever immunization are either local or general, or both. In the local category are redness, induration and sometimes an erysipeloid inflammatory reaction around the point of injection, lymphangitis, local adenitis, pain on activating the arm, fever, etc. The Dicks⁶ believe that the more highly susceptible an individual is, the more apt is he to have a

TABLE III
Nurses Who Developed Scarlet Fever and Who Had Five or More Doses of Scarlet Fever Toxin

Name	First Test	Other Tests	Immunized	Date of Scarlet Fever	Type of Disease
D R	pos 12/28/33	neg 1/12/34	5 injections	4/11/34	severe
M H	pos 1931	neg 1/11/32, pos 2/9/34, neg on discharge	5 "	2/8/34	mild
M S	pos 11/12/30	neg 1/28/31, pos 12/6/32, pos 12/27/32	5 "	12/5/32	mild
H H	pos 11/12/30	pos after last injection, neg 11/28/32	7 " (stopped because of reactions)	11/27/32	mild
W C	pos 1930	neg 10/28/30, pos 12/1/31	5 injections (severe reaction, 1930)	12/3/31	severe
L M	pos May '31	neg 10/25/32, neg 4/1/33	5 injections	3/31/33	mild
L A	pos 1936	pos 10/14/38	10 injections (2 series)	10/13/38	severe
S M	pos 1937	neg 12/19/32, neg 2/28/33	5 injections	2/27/33	moderate
R R	pos Sept '32	pos 1/22/35	5 "	1/21/35	severe
F S	pos 1934	pos 1/1/39, pos 7/14/39, pos 10/3/39, pos 10/28/39, pos 2/12/40	10 "	10/27/39	mild
I H	pos 5/5/38	neg 8/8/39, neg 11/15/39	6 "	11/11/39	mild
I I	pos 10/1/36	neg 5/20/37, neg 4/28/38, neg 1/3/39	8 "	1/6/38	severe with complications
C S	pos 7/30/32	neg 9/28/32, 1/1/33 and discharge	5 "	12/31/32	moderate
M W	pos 2/2/32	pos after 5 doses	5 "	4/11/32	moderate
H I	pos Oct '31	pos after inj, pos 11/26/31	5 "	11/25/32	mild
R S	pos Feb '29	pos 2/22/32, pos on discharge, pos 8/5/39	5 "	2/21/32	possible S F

reaction after the first dose It has been difficult for me to tell which of the five doses would cause a reaction, nor have I been able to foretell what kind of a reaction to expect Sometimes reactions will occur about superficially injected toxin

General reactions include malaise, nausea, headache, high fever, a scarlatiniform rash, vomiting, diarrhea, adenitis, arthritis, etc An arthritic, in my experience, is never desensitized by repeated injections of scarlet fever toxin to the point where he may not have reactions following subsequent increased injections of the toxin Arthritis, occurring during active immunization is due to the toxin (Healey¹¹) Sometimes, when it is injected deeply, absorption will take place too quickly and cause general symptoms Benson and Rankin⁴ reported that 14 per cent of 143 nurses immunized had constitutional symptoms

The total number of reactions in the group from City Hospital, Cleveland is noted in table 4

TABLE IV
Reactions

	Doses					Total No
	1	2	3	4	5 or more	
Reactions	58	77	84	77	68	364
Local	11	7	6	11	3	38
General	47	70	78	66	65	326

Number of nurses having reactions 131 (10.2%)

One hundred and thirty-one or 10.2 per cent of the nurses injected had reactions at some time or other Rappaport⁷ reported that 80 per cent or 31 of the nurses in the class of 1931 and 100 per cent or 35 in that of 1932 had reactions after the five doses of toxin Between 1924 and 1935, he tested 439 nurses, of whom 249 or 56.7 per cent were found susceptible and immunized He then started to inject smaller amounts more frequently He began with 150 skin test units, the subsequent doses were 300, 600, 1,200, 2,500, 5,000, 10,000, 20,000, 40,000 and 80,000 skin test units for each dose, respectively—a total of 159,750 skin test doses or 38.3 per cent more toxin than when the usual five doses (standard doses prior to 1940) were given

The amount of skin test doses of toxin now recommended by the Scarlet Fever Commission and injected subcutaneously is as follows 650, 2,500, 10,000, 30,000 and 100,000 skin test doses If the patient has a severe reaction to the initial dose or to the skin test, the subsequent injections should be decreased in amount and the number of injections increased Adrenalin is sometimes given with the toxin in doses of about 0.2 cc to 0.3 cc of a 1:1000 solution In a highly sensitive individual, one may start with one-fourth and increase to one-half of the original recommended dose, the next

time going back to the initial dose. If at any time there is a marked reaction, it might be advisable to revert to the last standard dose and then to start again with a quarter of that recommended. Each such susceptible is an individual problem.

NEGATIVE DICK TESTS AND DEVELOPMENT OF SCARLET FEVER

Seventy-six nurses were admitted with scarlet fever who had had negative Dick tests from one day to five years prior to contracting the disease (table 5). This was 2 per cent of the negative reactors.

TABLE V

Interval after Test Disease Contracted	No	Interval after Test Disease Contracted	No	Interval after Test Disease Contracted	No
1 day	2	1 month	9	1 yr	6
2 days	4	2 months	12	1 yr, 1 mo	1
3 "	1	3 "	11	1 " , 2 "	1
4 "	2	4 "	2	1 " , 6 "	2
5 "	1	5 "	4	1 " , 8 "	2
7 "	1	7 "	7	2 "	3
14 "	1	8 "	2	2 " , 5 "	1
				5 "	1

Despite their previous reports, the 76 individuals previously found negative were again Dick tested on admission to the hospital. Eight reactions could not be read accurately because of the rash, 25 had lost their immunity and were definitely positive reactors on admission, while 43 were still negative. This would give a corrected morbidity of 1 per cent in the exposed negative reactors. There may be some question about the results with one test dose, so that for the sake of accuracy, they were also tested to one, two, three and five skin test doses and found to be negative.

There are many reasons why a Dick test may be negative and erroneously so. This could explain some, but certainly not the majority of aberrant results. A negative reaction may occur if the Dick test material is not up to standard because it has not been kept properly and in accordance with the specifications.

There is only a minute amount of toxin in the skin test dose. This small amount may be easily neutralized or destroyed by some factor—soap, alcohol, iodine and the like. The skin test is a quantitative one, indicating the presence of a certain amount of antitoxin in the blood stream, thus, quantitative exposure greater than the usual may initiate scarlet fever in an individual who has protection against the ordinary doses of antigen to which he would customarily be exposed.

In doing a Dick test the skin must be dry and cleansed of alcohol and other disinfecting agents. Needles and syringes must be absolutely dry, the water in the barrel and needle should be blown out. Needles and

syringes should not be boiled in tap water. The dose of toxin must be accurately measured. The injection should be into the skin, and it should be read at the proper time. All the factors compared should be the same under all given circumstances.

The Dicks^a reported 20,956 persons with negative Dick tests, who, with but one exception had gone through at least one epidemic without contracting scarlet fever. Platou¹² collected reports on 20,000 immunized individuals and found that only one had developed the disease.

Speaking of failures to immunize, Anderson and Reinhardt⁵ stated that no biological phenomenon is mathematically exact, and that similar figures are encountered in dealing with other immune reactions.

DOES THE TOXIC ANTIGEN PROTECT ONLY AGAINST THE RASH?

Some individuals feel that all that is accomplished by giving scarlet fever toxin is to immunize against the toxin that produces the rash. They feel that immunized persons may still become ill with streptococci which cause scarlet fever. In fact, some believe that the number of colds, sore throats, etc. in this group is increased. As Place³ states, "whether the standard toxin will protect immunized persons against most clinical effects of scarlet fever and especially whether such immunized persons are protected against infection or only against the toxin" can be determined only by collective experiences under actual conditions of exposure. My own experience, however, has been quite fortunate. There is a rule at the City Hospital, Cleveland to the effect that nurses and all other personnel on any service contracting a sore throat or any upper respiratory infection are immediately isolated in the Contagious Disease Hospital. This has given me an opportunity to evaluate the results, and I can definitely conclude that there has been no increase in the number of nurses who have contracted scarlet fever or who have contracted streptococcal sore throat, in fact, I think there has been a very definite decrease. Only during epidemics, has there been a marked increase in the number of such patients admitted, and then we have those irrespective of whether they have been immunized or not. It is my impression that there has been a decrease in the number of nurses who have developed these types of acute upper respiratory infections.

Benson and Rankin⁴ gave definite figures on this point and concluded that there was no increase in the incidence of tonsillitis during an observation period from 1919-1933. In the 12 years before immunization, Place³ had 65 nurses, or 6.4 per cent, admitted with streptococcus infections other than scarlet fever, since immunization, there were 67 or 4.6 per cent.

HOW LONG DOES IMMUNITY LAST?

Anderson and Reinhardt⁵ state that immunity lasts at least three years. Our experiences do not extend beyond three years, after which nurses leave the hospital, and we lose control of the individual. In a small series (100)

we have been able to do Dick tests five years after a negative Dick test had been produced and have found that approximately 72 per cent were still negative. We have personal knowledge of an orphanage where the children have been immunized and where they have gone through several epidemics. The time interval has been at least 9 or 10 years, and the resident population still seems to be immunized and protected. If it is realized that there is a process of natural immunization constantly going on in children and that at least 65 per cent of adults may be immunized by the time they are between 20 and 30 years, it will be seen that an immunization procedure which protects children in the younger age group (from 5 to 6 years) may be sufficient to give them enough immunity so that with the additional stimulus obtained from frequent exposure, they may become permanently immunized against this disease. The Dicks⁶ state that the duration of immunity lasts approximately 12 years (90 per cent).

DO IMMUNIZED INDIVIDUALS BECOME CARRIERS?

This question is easily answered. The best place in the world to ascertain the presence of a carrier state is in a contagious disease hospital where there is a constant chance for the exposor to contact exposees, a most severe experimental test. If nurses were made carriers then we should have an increase in the number of scarlet fever cross infections in the contagious disease hospital. No other hospital has reported an increase, and we actually have had a decrease in hospital cross infections.¹¹

LARSON'S SCARLET FEVER TOXOID

Another type of antigen used to immunize against scarlet fever is ricinoleated toxoid introduced by Larson and his associates in 1926.¹⁵ They reported 77.3 per cent of positive skin tests becoming negative in eight days and 97 per cent in three weeks after the use of this antigen. Some of this vaccine material was obtained from Dr. Larson in 1926 and tried in a group of 41 nurses. The results are contained in table 6.

TABLE VI

Larson's Antigen (first dose 0.5 c.c., all others 1 c.c.) 41 susceptibles

	Reaction to Dick Toxin
11 received 1st and 2nd doses	15 neg 3 weeks later
26 remaining received 3rd and 4th doses	10 " 8 9 " "
16 remaining received 5th and 6th doses	5 " 3 " "
11 remaining received 7 to 17 doses	3 " "
	6 persistently positive

Two nurses who were negative reactors to the Dick test and had been immunized with Larson's toxin contracted scarlet fever, one had a mild attack; the other died. The histories of the two who contracted scarlet fever are outlined in table 7.

Protection was established in some of the susceptibles injected. The experiment was discontinued, however, because the reactions seemed nearly as severe as those following the Dick toxin, and the immunizing results were no better.

TABLE VII
Larson's Vaccine

Name	First Test	Other Tests	Immunized	Date of Scarlet Fever	Type of Disease
I M E K	pos 8/5/26 pos 10/4/26	neg 11/8/26	13 injections 5 "	1/9/27 1/25/27	Mild Died, hemorrhagic

GABRITCHEWSKY'S VACCINE

This is a mixture of killed streptococci and streptococci toxin. Benson and Rankin⁴ refer to several workers who used this material (Mstibowsky, Koischun and Spirina, Hoffmann, Sparrow, Zlatogoroff). The impression gained is that the morbidity and mortality rates of scarlet fever were lessened after its use. Zlatogoroff concluded that the vaccination had a favorable effect on both morbidity and mortality, but that this was short lived.

VELDEE'S FORMALINIZED TOXIN

Veldee¹⁶ has reported favorably on formalinized toxin. Futagi,¹⁷ using a toxoid, reported that over 84 per cent of a group of susceptibles given four injections of the solution were rendered Dick negative. Formalinized toxin was used by Anderson,⁸ who found that it caused so few reactions that it has been accorded a ready and popular acceptance in all groups to which it has been offered. He concluded that it had an appreciable immunizing value as measured both by Dick tests and by protection against clinically recognized scarlet fever. He felt, however, that this immunizing effect was not as great as that which followed the use of the standard five injections of Dick toxin. He concluded that as administered it is a less potent immunizing agent than Dick toxin, for only about 50 per cent of those susceptibles treated with formalinized toxin are rendered Dick negative in contrast to 90 to 95 per cent after the Dick toxin. Benson and Rankin⁴ believe that toxins tend to lose their antigenicity when formalinized.

STREPTOCOCCUS TOXINS

Park and Spiegel¹⁸ stated that it was quite possible that there were strains of streptococci which had the power to produce scarlet rash-producing toxins different from the standard Dick strains. Kirkbride and Wheeler¹⁹ reported on a person found susceptible to the Dochez toxin and not to the Dick or Williams toxin.

When the Dick test was first used by us in the Division of Contagious Diseases, City Hospital, Cleveland, a test was done in each scarlet fever patient on admission to the hospital. A positive test would invariably become negative within a month. In 1929, the results of the skin tests done on scarlet fever patients on admission were erratic. In 1933, the number of positive reactors became higher, but still there were many exceptions. Perhaps we dealt with epidemics caused by different strains of streptococci.²⁰ This would explain why nurses with negative Dick tests, nevertheless, develop scarlet fever.

It has been stated that the streptococci causing scarlet fever and erysipelas must be different, because clinically, erysipelas is a different disease from scarlet fever, although both are caused by streptococci. This conclusion does not follow. Erysipelas frequently follows, but rarely precedes

TABLE VIII
Nurses Who Had Streptococcus Toxins and Who Developed Scarlet Fever

Name	First Test	Other Tests	Immunized	Date of Scarlet Fever	Type of Disease
H H	pos 2/2/32	pos Dec '31, pos 4/4/32, pos 5/12/32, neg on discharge	5 injections	5/11/32	severely ill
V B	pos 10/13/31	neg 1, 2 and 5 skin test doses after injection, neg 12/31/31	6 "	12/30/31	mod severe
R G	pos 1/19/32, pos 2/2/32	pos after 1932, pos Feb '32, pos. 3/23/32	5 "	3/22/32	severe
E H	pos 10/5/31	neg 1/11/32, pos 2/2/33, neg on discharge	6 "	2/1/33	mod severe
A N	pos 2/2/32	pos after injection, pos 3/31/32	5 "	3/30/32	moderate
D R	pos 2/2/32	neg 4/4/32, neg 6/14/32	5 "	6/13/32	mod severe
V C	pos 10/13/31	neg 1/8/32, neg 1/23/32	6 "	1/22/32	severe

scarlet fever. There is antitoxin in the blood serum of erysipelas patients at the very time they get erysipelas. The clinical entity called erysipelas can best be explained by stating that it is really nothing more than a local, massive, allergic type of reaction occurring in an individual who has plenty of immunity against the streptococci, but who is sensitive to the protein products of the streptococcus organism.

It was decided to manufacture toxin from other strains and to determine if they could be used in immunization. Ten strains were used, including two Dick and one Dochez. Each strain was planted in 14 flasks of 0.5 per cent glucose broth. This was repeated daily for 14 days. Twenty-four hours after the first inoculation and daily thereafter, the toxin contained in one flask from each culture growth was harvested. There was great difficulty in standardization, but the conclusions were obvious. The Dick and Dochez strains produced a highly potent toxin in a very short time (24 to 48 hours).